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Multi-nutrient fortification of human milk for preterm infants (Review)

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TABLE OF CONTENTS

[Intervention Review]

Multi-nutrient fortification of human milk for preterm infants

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ABSTRACT

Background

Human breast milk-fed preterm infants can accumulate nutrient deficits leading to extrauterine growth restriction. Feeding preterm infants with multi-nutrient fortified human milk could increase nutrient accretion and growth rates and improve neurodevelopmental outcomes. Concern exists, however, that multi-nutrient fortifiers are associated with adverse events such as feed intolerance and necrotising enterocolitis.

Objectives

To determine whether multi-nutrient fortified human milk, compared with unfortified human milk, affects important outcomes (including growth rate and neurodevelopment) of preterm infants without increasing the risk of adverse effects (such as feed intolerance and necrotising enterocolitis).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 9), MEDLINE via PubMed (1966 to 26 September 2019), Embase (1980 to 26 September 2019), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 26 September 2019). We searched clinical trials databases, conference proceedings, and reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised and quasi-randomised controlled trials that compared feeding preterm infants with multi-nutrient (protein and energy plus minerals, vitamins, or other nutrients) fortified human breast milk versus unfortified (no added protein or energy) breast milk.

Data collection and analysis

We used the standard methods of Cochrane Neonatal. Two review authors separately evaluated trial quality, extracted data, and synthesised effect estimates using risk ratios (RRs), risk differences, and mean differences (MDs). We assessed the certainty of the body of evidence at the outcome level using "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) methods.

Main results

We identified 18 trials in which a total of 1456 preterm infants participated. These trials were generally small and methodologically weak. Meta-analyses provided low- to moderate-certainty evidence showing that multi-nutrient fortification of human milk increases in-hospital rate of weight gain (MD 1.76 g/kg/d, 95% confidence interval (CI) 1.30 to 2.22), body length (MD 0.11 cm/week, 95% CI 0.08 to 0.15), or head circumference (MD 0.06 cm/week, 95% CI 0.03 to 0.08) among preterm infants. Few data on growth and developmental outcomes assessed beyond infancy are available, and these do not show effects of multi-nutrient fortification. The data do not suggest other benefits

or harms and provide low-certainty evidence suggesting effects of multi-nutrient fortification on the risk of necrotising enterocolitis in preterm infants (typical RR 1.37, 95% CI 0.72 to 2.63; 13 studies, 1110 infants).

Authors' conclusions

Feeding preterm infants with multi-nutrient fortified human breast milk compared with unfortified human breast milk is associated with modest increases in in-hospital growth rates. Evidence is insufficient to show whether multi-nutrient fortification has any effect on long-term growth or neurodevelopment.

PLAIN LANGUAGE SUMMARY

Multi-nutrient fortification of breast milk for preterm infants

Review question: Do preterm infants (babies born early) grow and develop better when they are fed breast milk supplemented with extra protein and calories ("fortified")?

Background: Breast milk alone might not be enough to support preterm infants to grow and develop optimally. Extra nutrients, such as protein and energy (calories) from carbohydrates or fat, can be added to breast milk to make it about 10% to 20% more nutritious. These additional nutrients are called "fortifiers". Feeding preterm infants, especially very preterm infants (born before 32 weeks), fortified breast milk may mean that they take in more nutrients, grow faster, and develop better.

Study characteristics: We included 18 trials; most were small (involving 1456 infants in total) and had some design weaknesses that might bias their findings. The search is up-to-date as of September 2019.

Key results: Preterm infants who were fed fortified breast milk put on weight and grew in length and head size a little more quickly while they were in-hospital. The trials we included did not report a lot of information about the effects fortified breast milk might have on development and growth later in the baby's life. The data we have available do not suggest an effect of feeding fortified breast milk on outcomes when the child is older. The included trials provide no consistent evidence of other potential benefits or harms of fortified breast milk, including any effects on feeding or bowel problems.

Conclusion: Trial data show that multi-nutrient fortification increases growth rates of preterm infants during their first hospital admission but do not provide enough evidence to show any effects on longer-term growth or development. New trials are needed to discover more about this issue.

Certainty of evidence: We assessed this evidence for effects on growth as being of "low or moderate certainty" because the included trials were small, had methodological weaknesses, and reported findings that were inconsistent with each other. This means that further research is very likely to have an important impact on the estimates of effect and on our confidence in study findings.

SUMMARY OF FINDINGS

Summary of findings 1. Multi-nutrient fortification of human milk for preterm infants

Patient or population: preterm infants
Setting: healthcare setting
Intervention: fortified breast milk
Comparison: unfortified breast milk

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with unfortified breast milk	Risk with fortified breast milk			
Weight gain (g/kg/d)	Comparator	Mean weight gain was 1.76 g/kg/d more (1.30 more to 2.22 more)	-	951 (14 RCTs)	⊕⊕⊖⊖ Low[a,b]
Length gain (cm/week)	Comparator	Mean length gain was 0.12 cm/week more (0.07 more to 0.17 more)	-	741 (10 RCTs)	⊕⊕⊖⊖ Low[a,b]
Head growth (cm/week)	Comparator	Mean head growth was 0.08 cm/week more (0.04 more to 0.12 more)	-	821 (11 RCTs)	⊕⊕⊕⊖ Moderate[b]
Mental development index (MDI) at 18 months	Comparator	Mean MDI was 2.2 more (3.35 fewer to 7.75 more)	-	245 (1 RCT)	⊕⊕⊕⊖ Moderate[c]
Psychomotor development index (PDI) at 18 months	Comparator	Mean PDI was 2.4 more (1.9 fewer to 6.7 more)	-	245 (1 RCT)	⊕⊕⊕⊖ Moderate[c]
Necrotising enterocolitis	Study population		RR 1.37 (0.72 to 2.63)	1110 (13 RCTs)	⊕⊕⊖⊖ Low[b,c]
	26 per 1000	40 per 1000 (19 to 68)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

[a]Downgraded one level for inconsistency in effect estimates (moderate or high heterogeneity; $I^2 > 50\%$).
[b]Downgraded one level for serious study limitations due to high risk of bias (uncertainty about methods used to generate random sequence, conceal allocation, and blind assessments) in most trials.
[c]Downgraded one level for imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit).

BACKGROUND

Description of the condition

Most preterm infants accumulate nutrient deficits during the initial neonatal unit admission (Embleton 2001; Cooke 2004). By the time they are ready to go home, typically at around 36 to 40 weeks' postmenstrual age, many infants, especially those born very preterm or very low birth weight (VLBW), are growth-restricted relative to their term-born peers (Ehrenkranz 1999; Steward 2002; Clark 2003; Dusick 2003). Although very preterm or VLBW infants usually attain some "catch-up" growth following hospital discharge, growth deficits can persist through childhood and adolescence and into adulthood (Dusick 2003; Euser 2008). Slow postnatal growth is associated with neurodevelopmental impairment and poorer cognitive and educational outcomes (Brandt 2003; Leppanen 2014). Preterm infants who have accumulated mineral deficits have higher risks of metabolic bone disease and slow skeletal growth compared with infants born at term, although uncertainty remains about long-term effects on bone mass and health (Fewtrell 2011). Furthermore, concern exists that growth restriction in utero and during infancy may have consequences for long-term metabolic and cardiovascular health (Embleton 2013; Lapillonne 2013).

Description of the intervention

Multi-nutrient fortification of breast milk

Human breast milk is the recommended enteral nutrition for infants (Section on Breastfeeding 2012). Breast milk alone, however, might not meet the recommended nutritional needs of growing preterm infants (Embleton 2007; Agostoni 2010). International consensus guidelines state that "standard" volumes of breast milk (about 150 to 180 mL/kg/d) do not provide the recommended amount of energy (110 to 135 kcal/kg/d) or protein (3.5 to 4.5 g/kg/d) to meet the metabolic needs of preterm infants (AAP 2004; Agostoni 2010). The strategy most commonly employed in neonatal care facilities in high-income countries to address these deficits is to supplement human breast milk with extra nutrients, usually in the form of a powder or liquid "multi-nutrient fortifier" (Gregory 2012; Klingenberg 2012; Cormack 2013; Tudehope 2013; Dutta 2015). Most commercially available multi-nutrient fortifiers are derived from cow's milk, but fortifiers derived from human milk have been developed (Rochow 2015).

Fortifiers are intended to be mixed with expressed breast milk with the aim of achieving about 10% to 20% nutrient enrichment while maintaining optimal protein-to-energy ratios to promote lean mass growth (Embleton 2007; Agostoni 2010; Moya 2012; Section on Breastfeeding 2012; Tudehope 2013). Multi-nutrient fortification may be especially important for infants who receive donated (donor) human breast milk, which typically contains lower levels of protein, energy, and minerals than their own mother's expressed breast milk (Arslanoglu 2013). Commercially available fortifiers are expensive, and their use is limited in resource-poor settings in low- or middle-income countries (Chawla 2008; Kler 2015). An alternative strategy employed in resource-limited settings is to add cow's milk formula powder to human breast milk to nutrient-enrich by the required amount (Gross 1993).

Targeted and adjustable fortification

Nutrient (especially energy and protein) content of expressed breast milk varies between mothers and between different batches of a woman's expressed breast milk (de Halleux 2013). If the nutrient levels in expressed breast milk are measured, the amount of fortifier added can be *targeted* (also referred to as *individualised*) to achieve a desired content (Rochow 2013; Rochow 2015). The level of fortification may be *adjusted* in response to the metabolic demands and responses of individual infants, for example, by titration to the infant's blood urea nitrogen level (Arslanoglu 2010).

How the intervention might work

Multi-nutrient fortification, that is, feeding preterm infants with human breast milk fortified with protein and non-protein energy (carbohydrate or fat), as well as minerals and other nutrients, may be expected to promote nutrient accretion and growth (increase in weight, length, and head circumference). High levels of nutrient intake during this critical period might be especially important for infants who are not able to consume large quantities of milk, who have slow growth, or who have ongoing additional nutritional and metabolic requirements (Agostoni 2010).

A potential disadvantage of multi-nutrient fortification is that increasing nutrient density and osmolarity of human breast milk might interfere with gastric emptying and intestinal peristalsis, resulting in feed intolerance or increasing the risk of necrotising enterocolitis (Ewer 1996; McClure 1996; Gathwala 2008; Yigit 2008; Morgan 2011). Several cases of subacute bowel obstruction due to impaction with "milk curd" have been reported in very preterm infants fed multi-nutrient fortified human breast milk, putatively due to the high calcium content causing fat malabsorption (Flikweert 2003; Wagener 2009; Stanger 2014).

Furthermore, investigators have been concerned that accelerated weight gain during this critical early phase might be associated with altered fat distribution and related "programmed" metabolic consequences that may increase long-term risks of insulin resistance and hypertension (Euser 2005; Singhal 2007; Euser 2008).

Why it is important to do this review

Given the potential for multi-nutrient fortification of human breast milk to affect important outcomes for preterm infants, this review aims to detect, appraise, and synthesise available evidence from randomised controlled trials to inform practice and research.

OBJECTIVES

To determine whether multi-nutrient fortified human milk, compared with unfortified human milk, affects important outcomes (including growth rate and neurodevelopment) of preterm infants without increasing the risk of adverse effects (such as feed intolerance and necrotising enterocolitis).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials, including cluster-randomised controlled trials. We did not include cross-over trials.

Types of participants

Preterm (< 37 weeks' gestational age) and low birth weight (< 2500 g) infants receiving human breast milk.

Types of interventions

Multi-nutrient fortification of human breast milk (expressed maternal or donor or both) with protein *and* non-protein energy (carbohydrate or fat). Multi-nutrient fortifiers additionally could contain minerals, iron, vitamins, or other nutrients. Multi-nutrient fortifiers could be cow (or another animal) milk-based or human milk-based. The control group should not have received protein *or* non-protein energy fortification but could have received milk supplemented with minerals, iron, vitamins, or other nutrients.

Eligible trials should have planned to allocate the trial intervention for a sufficient period (at least two weeks) to allow measurable effects on growth. Infants in comparison groups within each trial should have received similar care other than the level of fortification of breast milk. No between-group differences in target levels of volume of milk intake should have occurred.

We did not include trials of:

- targeted or adjustable fortification (vs standard fortification);
- early versus later introduction of multi-nutrient fortifier; or
- human milk-based versus cow milk-based fortifier

Types of outcome measures

Primary outcomes

- Growth: weight, length, head growth, skinfold thickness, body mass index, and measures of body composition (lean/fat mass) and growth restriction (proportion of infants who remain < 10th percentile for the index population distribution of weight, length, or head circumference)
- Neurodevelopmental outcomes assessed after 12 months post term: neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability. We defined neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy, developmental quotient more than two standard deviations below the population mean, and blindness (visual acuity < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification)

Secondary outcomes

- Duration of hospital admission (weeks)
- Feed intolerance that results in cessation of or reduction in enteral feeding
- Necrotising enterocolitis (modified Bell stage 2/3; Walsh 1986)
- Measures of bone mineralisation such as serum alkaline phosphatase level, or bone mineral content assessed by dual energy X-ray absorptiometry (DEXA) and clinical or radiological evidence of rickets on long-term follow-up (restricted to trials without mineral supplementation of the control group)
- Measures of long-term metabolic or cardiovascular health, including insulin resistance, obesity, diabetes, and hypertension

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal.

Electronic searches

We updated the searches to identify reports of trials available since the searches in December 2014 and February 2016 (Appendix 1). We searched these databases on 26 September 2019: the Cochrane Central Register of Controlled Trials, in the Cochrane Library (2018, Issue 9), MEDLINE ALL (Ovid), Embase (Ovid), the Cumulative Index to Nursing and Allied Health (CINAHL) Complete (EBSCO), and Maternity and Infant Care (Ovid). We imported and de-duplicated search results against previous search results from December 2014. We did not apply any language restrictions.

We searched clinical trials registries for ongoing or recently completed trials on 30 September 2019 (ClinicalTrials.gov and the World Health Organization's International Trials Registry Platform - https://www.who.int/ictrp/en/).

Searching other resources

We examined the references in studies identified as potentially relevant. We also searched abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2019), the European Society for Paediatric Research (1995 to 2019), the UK Royal College of Paediatrics and Child Health (2000 to 2019), and the Perinatal Society of Australia and New Zealand (2000 to 2019). We considered trials reported only as abstracts to be eligible if sufficient information was available from the report, or from contact with study authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

One review author (JVEB) screened titles and abstracts of all records identified by the search and coded records as "order" or "exclude". A second review author (LL) assessed all records coded as "order" and made the final decision about which records were ordered as full-text articles. JVEB read the full texts and used a checklist to assess each article's eligibility for inclusion on the basis of pre-specified inclusion and exclusion criteria. WM checked these decisions.

Data extraction and management

Two review authors (JVEB and LL) extracted data independently using a data collection form to aid extraction of information on design, methods, participants, interventions, outcomes, and treatment effects from each included study. We discussed disagreements until we reached consensus. If data from the trial reports were insufficient, we contacted trialists for further information.

Assessment of risk of bias in included studies

Two review authors (JVEB and LL) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2019) for the following domains.

- Sequence generation (selection bias).

- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).

Any disagreements were resolved by discussion or by a third assessor (WM).

See Appendix 2 for a description of risk of bias for each domain.

Measures of treatment effect

We analysed treatment effects in the individual trials using Review Manager 5.3 and reported risk ratios (RRs) and risk differences (RDs) for dichotomous data, and mean differences (MDs) for continuous data, with respective 95% confidence intervals (CIs). We determined the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. For cluster-randomised trials (had we identified any for inclusion), we planned to undertake analyses at the level of the individual while accounting for clustering in the data using methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Dealing with missing data

We requested additional data from trial investigators when data on important outcomes were missing or were reported unclearly. When data were still missing, we examined the impact of this on effect size estimates in sensitivity analyses.

Assessment of heterogeneity

We examined treatment effects in individual trials and heterogeneity between trial results by inspecting the forest plots if more than one trial was included in a meta-analysis. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate (I^2 > 50%) or high (I^2 > 75%) heterogeneity, we explored possible causes (e.g. differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

For outcomes with 10 or more trials contributing events in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate this, including exploration of differences in study design, participants, interventions, or completeness of outcome assessments.

Data synthesis

We used fixed-effect models for meta-analysis (as per Cochrane Neonatal recommendations). When moderate or high heterogeneity existed, we planned to examine the potential causes in subgroup and sensitivity analyses.

Subgroup analysis and investigation of heterogeneity

We planned to undertake these subgroup analyses, when possible.

- Very preterm (< 32 weeks' gestation) or VLBW (< 1500 g) infants (versus infants 32 to 36 weeks' gestation or birth weight 1500 to 2499 g).
- Fortification of donor breast milk (versus maternal expressed breast milk).
- Trials using fortifier extracted from human milk (versus cow milk-based fortifier).
- Trials supplementing breast milk with infant formula (versus cow milk-based fortifier).
- Trials conducted in low- and middle-income countries versus those in high-income countries (see http://data.worldbank.org/about/country-classifications).

Sensitivity analysis

If meta-analyses were moderately or highly heterogeneous (I^2 > 50%), we planned sensitivity analyses to determine whether findings were affected (and heterogeneity reduced) by including only studies at low overall risk of bias, defined as adequate randomisation and allocation concealment, masking of intervention and measurement, and < 10% loss to follow-up for outcome assessment.

Summary of findings and assessment of the certainty of evidence

We used the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach, as outlined in the Grade Handbook (Schünemann 2013), to assess the certainty of evidence for these outcomes: growth, development, and necrotising enterocolitis.

Two review authors (WM and JVEB) independently assessed the certainty of evidence for each of the outcomes. We considered evidence from randomised controlled trials as high certainty but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias (see Appendix 3). We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the certainty of evidence (GRADEpro GDT).

Summary of findings and assessment of the certainty of the evidence

We used the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach, as outlined in the Grade Handbook (Schünemann 2013), to assess the certainty of evidence of these outcomes: growth, development, necrotising enterocolitis.

Two review authors (WM and JVEB) independently assessed the certainty of the evidence for each of the outcomes. We considered evidence from randomised controlled trials as high certainty but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias (see Appendix 3). We used the GRADEpro GDT Guideline Development

Tool to create nine 'Summary of findings' tables to report the certainty of the evidence (GRADEpro GDT).

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

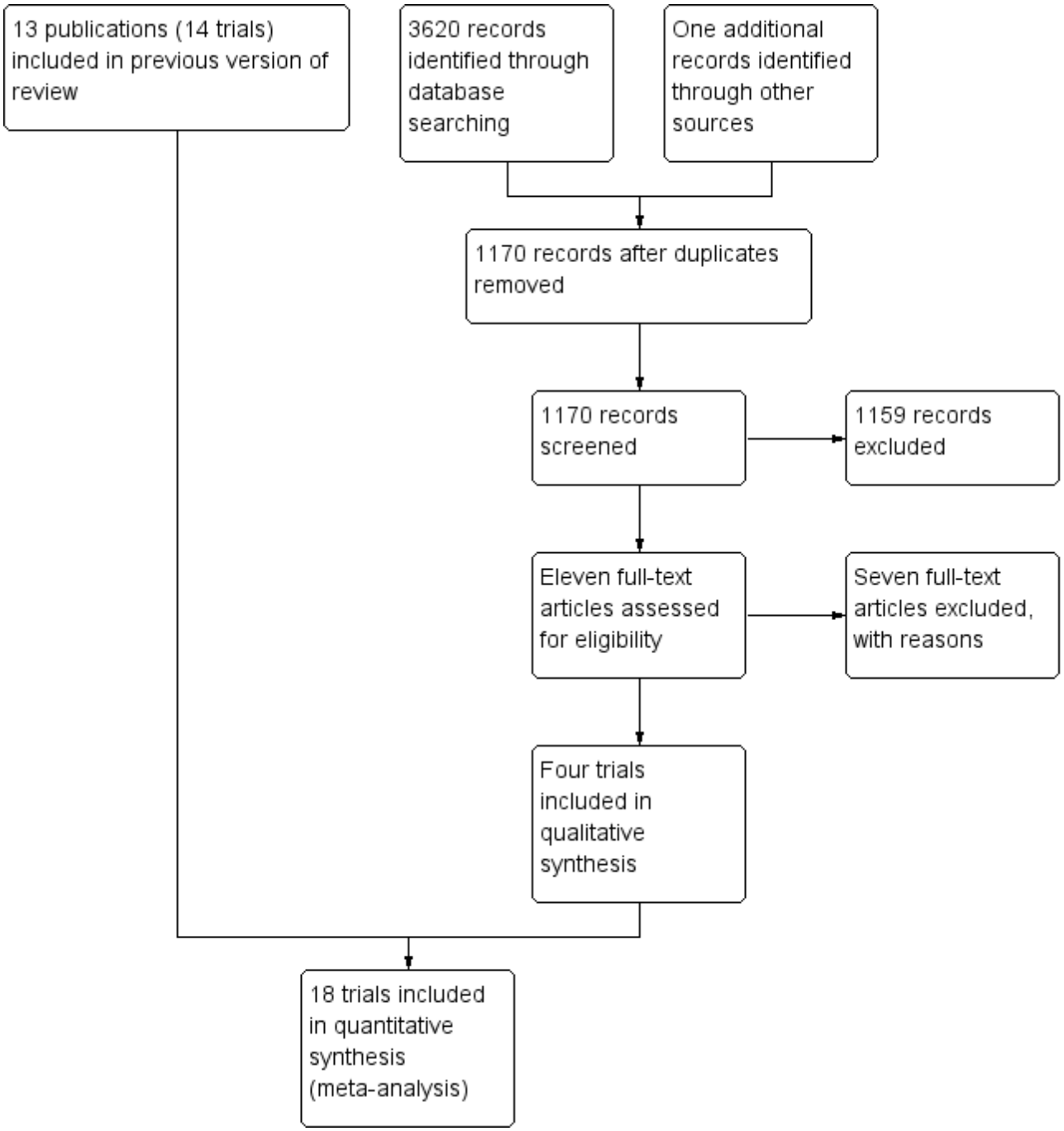
Results of the search

After searching all of the databases and trial registers, we had retrieved 3620 records. We de-duplicated these against results from previous searches carried out for this review. This left 1170 unique records. We identified one additional record from a different source and screened 1171 titles and abstracts, of which we excluded 1159 as irrelevant.

We assessed 11 studies as full text; we included four of these and excluded the remaining seven.

See Figure 1 for the study selection process and Characteristics of included studies and Characteristics of excluded studies for further detail on the studies we considered for inclusion in this review.

Figure 1. Study flow diagram.



Included studies

We included in this review 18 trials (17 primary publications) in which 1456 infants participated (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Pettifor 1989; Polberger 1989; Porcelli 1992; Zuckerman 1994; Lucas 1996; Wauben 1998; Nicholl 1999; Faerk 2000; Bhat 2003; Mukhopadhyay 2007; Gathwala 2012; Einloft 2015; El Sakka 2016; Gupta 2018; Adhisivam 2019). Sample sizes ranged between 14 and 275 participants.

All trials were conducted in specialist paediatric hospitals, typically in neonatal intensive care units. Fourteen were single-centre trials (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Pettifor 1989; Porcelli 1992; Zuckerman 1994; Nicholl 1999; Bhat 2003; Mukhopadhyay 2007; Gathwala 2012; Einloft 2015; El Sakka 2016; Gupta 2018; Adhisivam 2019), and each of the remaining four was conducted at two centres (Polberger 1989; Lucas 1996; Wauben 1998; Faerk 2000).

The trials were conducted in Europe (Polberger 1989; Porcelli 1992; Lucas 1996; Nicholl 1999; Faerk 2000), Asia (Bhat 2003; Mukhopadhyay 2007; Gathwala 2012; Gupta 2018; Adhisivam 2019), North America (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Wauben 1998), Africa (Pettifor 1989; Zuckerman 1994; El Sakka

2016), and South America (El Sakka 2016). Publication dates span four decades, ranging from 1986 to 2019.

Participants

All trials included preterm or LBW infants and excluded those with major congenital abnormalities. Eleven trials restricted participation to very preterm or VLBW infants (Modanlou 1986; Pettifor 1989; Polberger 1989; Zuckerman 1994; Nicholl 1999; Faerk 2000; Bhat 2003; Mukhopadhyay 2007; Einloft 2015; El Sakka 2016; Gupta 2018). Adhisivam 2019 enrolled "healthy preterm infants" without specifying a birth weight criterion. Other trials specified the upper birth weight eligibility threshold as:

- 1600 g (Gross 1987 (1); Gross 1987 (2));
- 1800 g (Gathwala 2012; Wauben 1998);
- 1850 g (Lucas 1996); or
- 2000 g (Porcelli 1992).

Interventions

Six trials used only maternal breast milk (Pettifor 1989; Zuckerman 1994; Wauben 1998; Einloft 2015; El Sakka 2016; Gupta 2018) One trial used only donor human breast milk (Adhisivam 2019). Seven trials used a mixture of mother's own milk and donor milk (Gross 1987 (1); Gross 1987 (2); Polberger 1989; Porcelli 1992; Nicholl 1999; Faerk 2000; Mukhopadhyay 2007). Investigators in the remaining four trials used formula to supplement maternal milk feeds to the required volume (Modanlou 1986; Lucas 1996; Bhat 2003; Gathwala 2012).

Types of multi-nutrient fortification added to milk for infants in the intervention groups varied. Most trials used a commercially available, cow's milk-based, powdered preparation containing varying amounts of protein, fat, carbohydrate, minerals, electrolytes, and trace minerals.

- Similac Human Milk Fortifier (Ross Laboratories): Gross 1987 (1); Gross 1987 (2). Gross 1987 (1) included a third group of infants receiving human milk fortified with formula (see below).
- FM85 (Nestlè): Porcelli 1992; Einloft 2015.
- Enfamil HMF (Mead Johnson): Lucas 1996.
- Nutriprem (Cow & Gate Nutricia): Nicholl 1999.
- Eoprotin (Milupa): Faerk 2000.
- Lactodex HMF (Raptakos Brett): Mukhopadhyay 2007; Gathwala 2012; Adhisivam 2019.
- Trial-specific multi-nutrient fortifier (Wyeth-Ayerst): Wauben 1998.

Four trials used preterm formula powder as the multi-nutrient fortifier.

- Similac Special Care (Ross Laboratories): Gross 1987 (1).
- Alprem (Nestlè): Zuckerman 1994.
- Bebelac Premature (Nutricia): El Sakka 2016.
- Simyl LBW (FDC Ltd): Gupta 2018.

Three trials did not specify the name or manufacturer of the multi-nutrient fortifier used: Modanlou 1986; Polberger 1989; Bhat 2003.

Participants received the intervention when tolerating a specified quantity of milk feeds daily, typically at least 100 mL/kg, or when receiving "full" enteral feeds, typically 150 mL/kg/d. The duration of intervention varied between trials, but the intervention was usually provided until a pre-specified body weight was attained (most commonly, 1800 to 2000 g), or until a pre-specified postmenstual age (36 weeks), or until discharge home from hospital.

Comparators

Most trials added vitamins, minerals, or other nutrients to control infant feeds as part of standard hospital practice. Five trials provided all infants with additional vitamin D (Pettifor 1989; Porcelli 1992; Zuckerman 1994; Faerk 2000; El Sakka 2016). Eight trials provided all infants with multi-vitamins, iron, and minerals (added to feeds for infants in the control group, and included in the fortifier or added separately for infants in the intervention group) (Gross 1987 (1); Gross 1987 (2); Polberger 1989; Lucas 1996; Wauben 1998; Einloft 2015; Gupta 2018; Adhisivam 2019). Researchers in five trials gave no supplements at all to control group infants (Modanlou 1986; Nicholl 1999; Bhat 2003; Mukhopadhyay 2007; Gathwala 2012).

Outcomes

Fourteen trials reported in-hospital growth rate data (Modanlou 1986; Gross 1987 (1); Gross 1987 (2); Pettifor 1989; Polberger 1989; Porcelli 1992; Lucas 1996; Wauben 1998; Nicholl 1999; Mukhopadhyay 2007; Einloft 2015; El Sakka 2016; Gupta 2018; Adhisivam 2019). Only Lucas 1996 reported growth and neurodevelopmental data at follow-up beyond hospital discharge.

Excluded studies

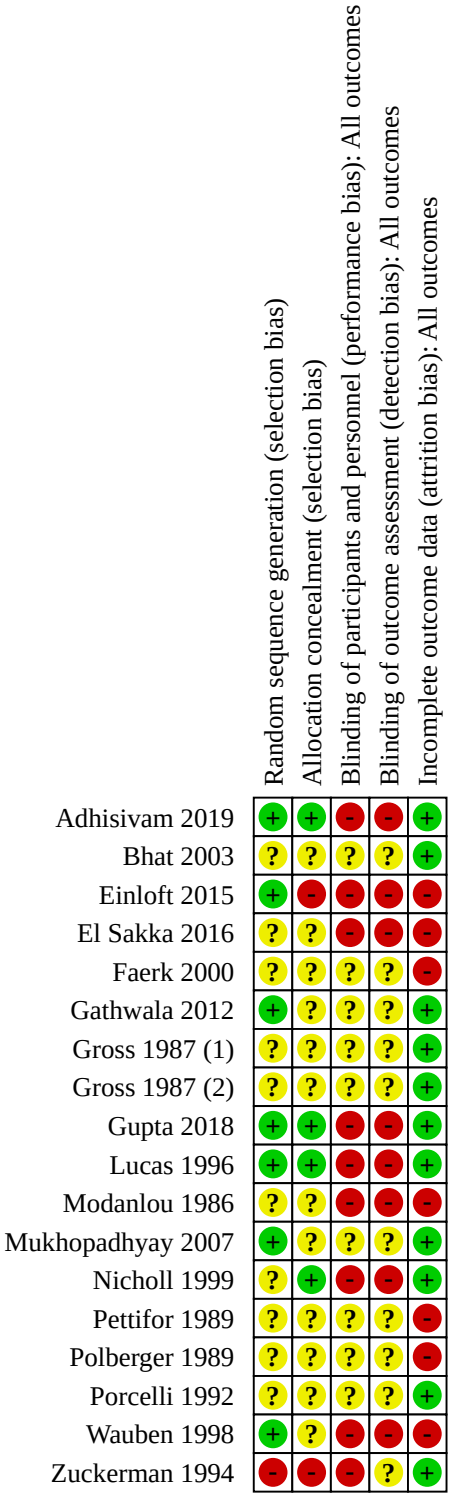
See Characteristics of excluded studies for details. We excluded:

- Carey 1987; Greer 1988; and Atchley 2019 because they used fortification with protein only (no fortification with fat or carbohydrate);
- Arco 2002; Tarcan 2004; Arslanoglu 2009; Reali 2010; Hair 2014; and Ramaswamy 2019 because they were not randomised controlled trials;
- Abrams 2014 because it compared human versus cow's milk-based protein fortification rather than fortification versus no fortification; and
- Chan 2000; Miura 2009; and Kim 2015 because these trials conducted comparisons of different fortifiers, with no control group receiving unfortified milk.

Risk of bias in included studies

See Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Risk of selection bias was largely "unclear". Seven trials described adequate methods of random sequence generation (Lucas 1996; Wauben 1998; Mukhopadhyay 2007; Gathwala 2012; Einloft 2015; Gupta 2018; Adhisivam 2019). Four explicitly described adequate allocation concealment methods (Lucas 1996; Nicholl 1999; Gupta 2018; Adhisivam 2019). Zuckerman 1994 was at high risk of selection bias, as investigators performed group allocation in a quasi-randomised fashion (odd and even hospital numbers).

Blinding

Nine trials were known to be at high risk of performance and selection bias as reports stated that personnel and outcome assessors were not masked (Modanlou 1986; Zuckerman 1994; Lucas 1996; Wauben 1998; Nicholl 1999; Einloft 2015; El Sakka 2016; Gupta 2018; Adhisivam 2019). Risk of performance and selection bias was "unclear" in the other trial reports.

Incomplete outcome data

We judged seven trials to be at high risk of attrition bias (Modanlou 1986; Pettifor 1989; Polberger 1989; Wauben 1998; Faerk 2000; Einloft 2015; El Sakka 2016), and the other trials to be at low risk.

Other potential sources of bias

Authors of three trial reports were employees of the manufacturer of the fortifier used (Modanlou 1986; Lucas 1996; Wauben 1998). The manufacturer of the fortifier funded three trials (Pettifor 1989; Lucas 1996; Einloft 2015).

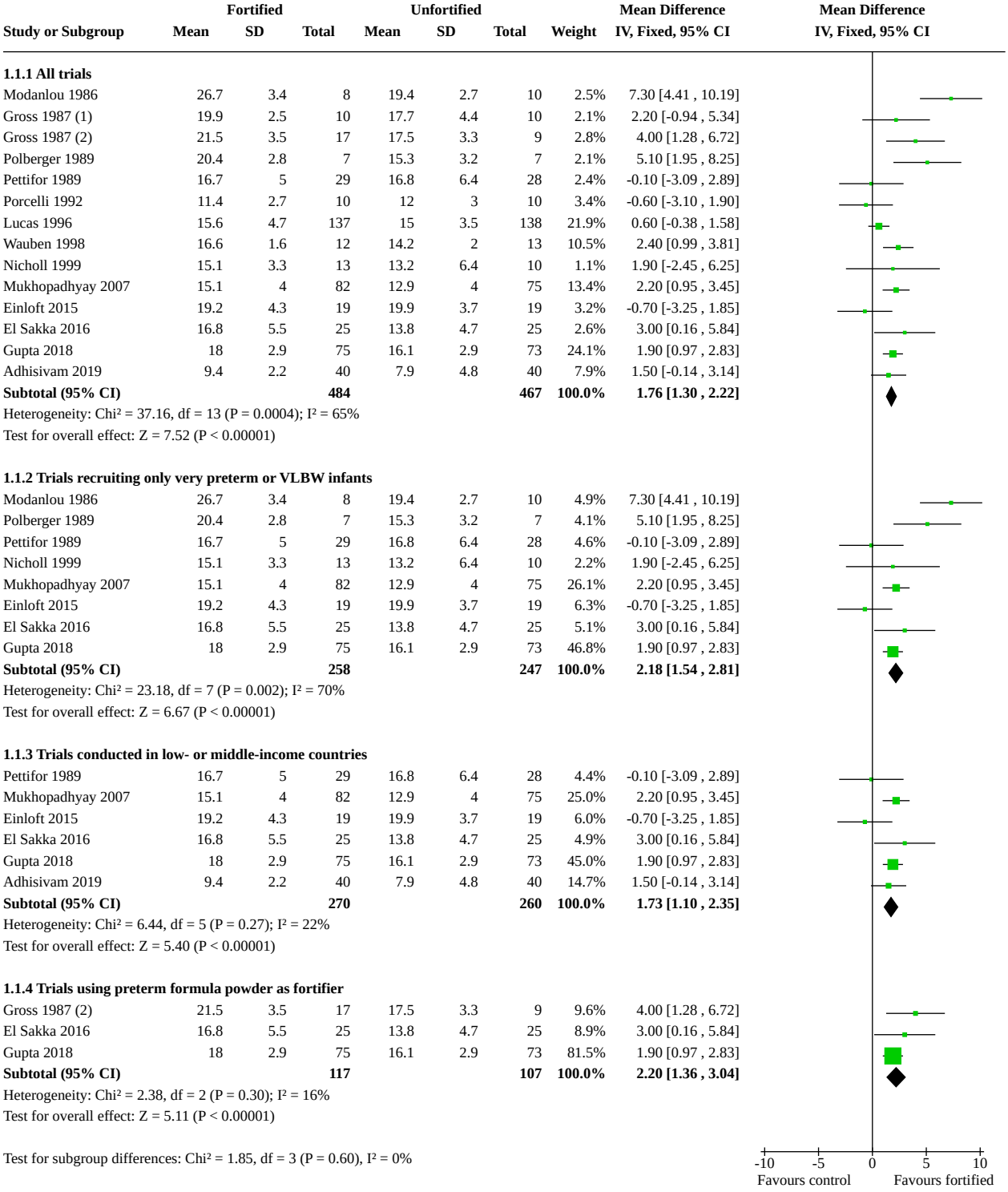
Effects of interventions

See: **Summary of findings 1** Multi-nutrient fortification of human milk for preterm infants

Growth rates (Outcomes 1.1 to 1.6)

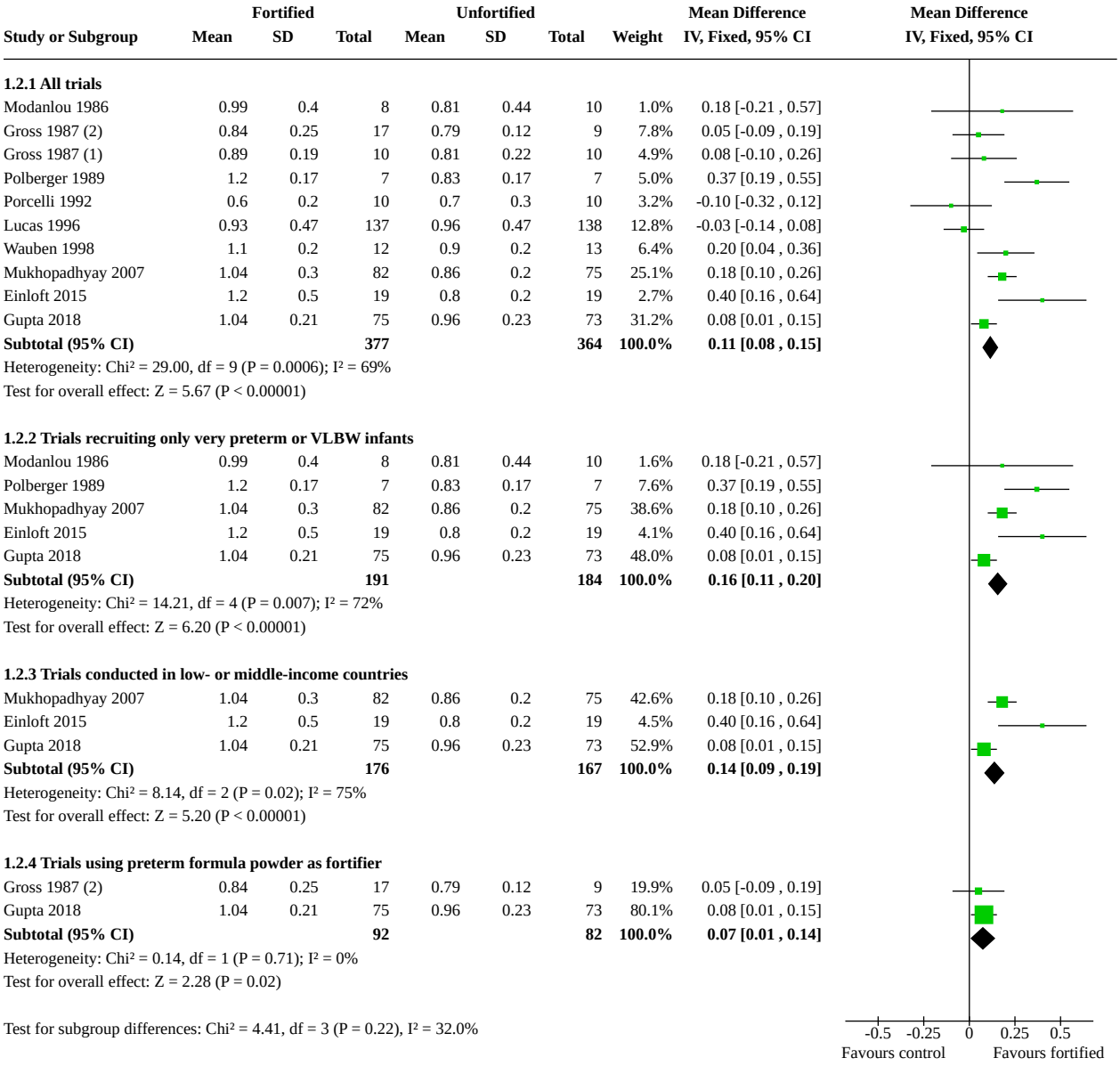
Weight gain (Analysis 1.1). Meta-analysis of data from 14 trials including 951 infants showed a higher rate of weight gain in the intervention (fortifier) group (mean difference (MD) 1.76, 95% confidence interval (CI) 1.30 to 2.22 g/kg/d). Moderate heterogeneity was present in this analysis (I^2 = 65%) (Figure 3). This was not explained in sensitivity analyses. The funnel plot was not asymmetrical. We assessed the certainty of evidence as "low" using GRADE methods, downgraded for risk of bias in included trials and for unexplained heterogeneity in the meta-analysis (Summary of findings 1).

Figure 3. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.1 Weight gain (g/kg/d).



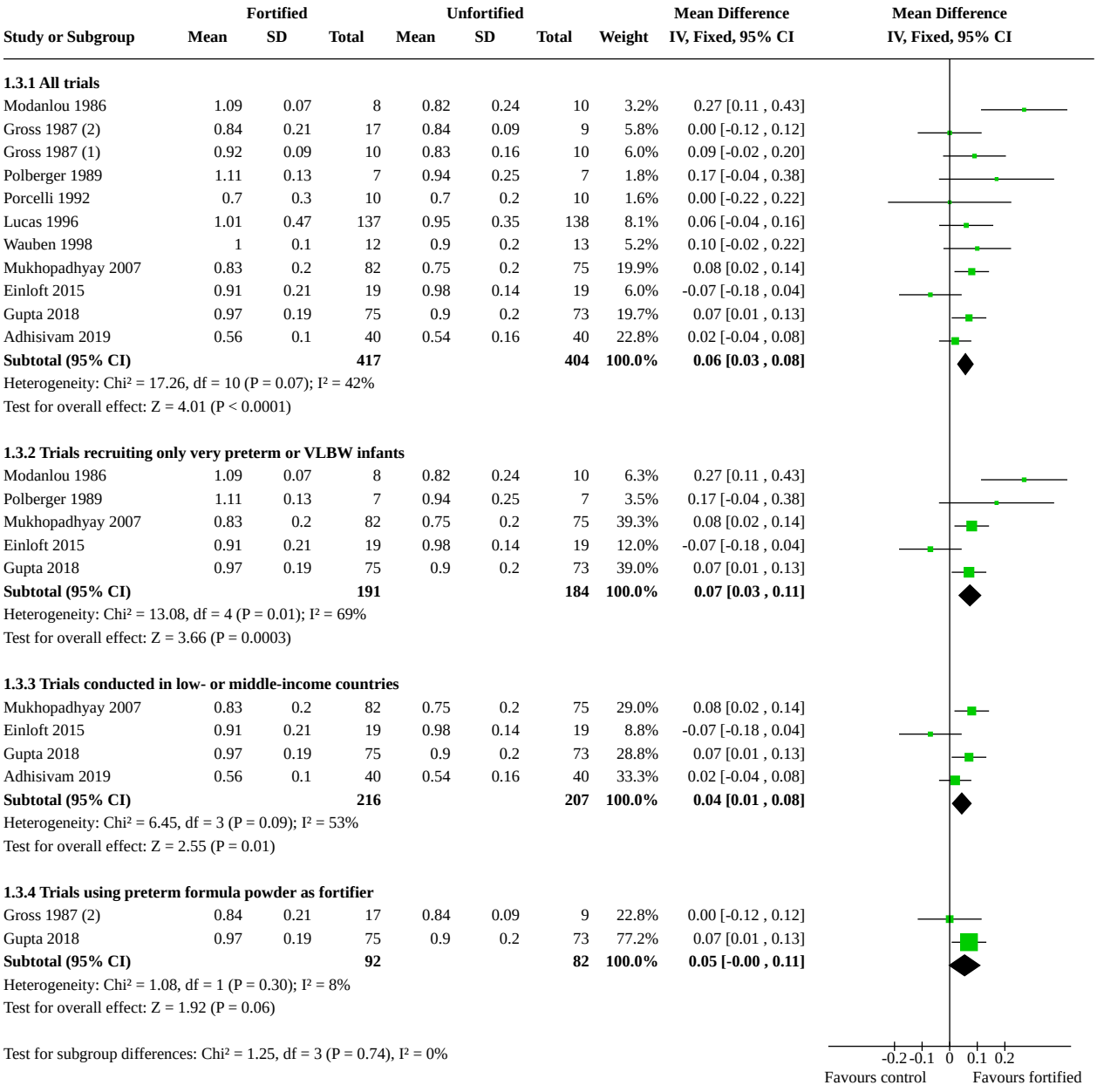
Length gain (Analysis 1.2). Meta-analysis of data from 10 trials including 741 infants showed a higher rate of length gain in the intervention group (MD 0.11, 95% CI 0.08 to 0.15 cm/week). Moderate heterogeneity was present in this analysis (I^2 = 69%) (Figure 4). This was not explained in sensitivity analyses. The funnel plot was not asymmetrical. We assessed the certainty of evidence as "low" using GRADE methods, downgraded for risk of bias in included trials and for unexplained heterogeneity in meta-analysis (Summary of findings 1).

Figure 4. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.2 Length gain (cm/week).



Head growth (Analysis 1.3). Meta-analysis of data from 11 trials including 821 infants showed a higher rate of head growth in the intervention group (MD 0.06, 95% CI 0.03 to 0.08 cm/week). We detected low heterogeneity in this analysis (I^2 = 42%) (Figure 5). The funnel plot was not asymmetrical. We assessed the certainty of evidence as "moderate" using GRADE methods, downgraded for risk of bias in included trials (Summary of findings 1).

Figure 5. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.3 Head growth (cm/week).



Weight at 12 to 18 months (Analysis 1.4). We obtained data from Lucas 1996 and Wauben 1998 (270 infants). Neither trial nor a meta-analysis of their data showed an effect (MD -0.03, 95% CI -0.31 to 0.25 kg).

Length at 12 to 18 months (Analysis 1.5). We obtained data from Lucas 1996 and Wauben 1998 (270 infants). Neither trial nor a meta-analysis of their data showed an effect (MD -0.19, 95% CI -0.98 to 0.60 cm).

Head circumference at 12 to 18 months (Analysis 1.6). We obtained data from Lucas 1996 and Wauben 1998 (270 infants). Neither trial nor a meta-analysis of their data showed an effect (MD -0.10, 95% CI -0.37 to 0.18 cm).

Neurodevelopmental outcomes after 12 months of age (Outcomes 1.7 and 1.8)

One trial (245 infants) reported data (Lucas 1996). This trial showed no statistically significant differences in:

- mental development index at 18 months (Analysis 1.7): MD 2.20 (95% CI -3.35 to 7.75); or
- psychomotor development index at 18 months (Analysis 1.8): MD 2.40 (95% CI -1.90 to 6.70).

We assessed the certainty of evidence as "moderate" using GRADE methods, downgraded for imprecision of estimates of effect (Summary of findings 1).

Length of hospital stay in weeks (Outcome 1.9)

Meta-analysis of data from six trials including 526 infants did not show a difference (MD -0.07, 95% CI -0.35 to 0.21 weeks; Analysis 1.9).

Feed intolerance (Outcome 1.10)

Meta-analysis of data from seven trials including 453 infants did not show an effect (typical RR 1.05, 95% CI 0.65 to 1.67; Analysis 1.10).

Necrotising enterocolitis (Outcome 1.11)

Meta-analysis of data from 13 trials including 1110 infants did not show an effect (typical RR 1.37, 95% CI 0.72 to 2.63; Analysis 1.11). Low heterogeneity was present in this analysis (I^2 = 0%). We assessed the certainty of evidence as "low" using GRADE methods, downgraded for high risk of bias in most trials and for imprecision of estimates of effect (Summary of findings 1).

Measures of bone mineralisation (Outcomes 1.12 and 1.13)

Serum alkaline phosphatase (Analysis 1.12). Meta-analysis of data obtained from six trials (restricted to trials without mineral supplementation of the control group) showed that the intervention group had lower serum alkaline phosphatase (ALP) levels (Modanlou 1986; Pettifor 1989; Zuckerman 1994; Mukhopadhyay 2007; Gathwala 2012; Einloft 2015): weighted mean difference (WMD) -142 (95% CI -204 to -80) IU/L. Moderate heterogeneity was present in this analysis (I^2 = 60%). Bhat 2003 did not report peak ALP levels but did state that the intervention group included fewer infants who developed high ALP levels (> 450 IU/L) than were included in the control group (without mineral supplementation).

Bone mineral content (Analysis 1.13). Only Pettifor 1989 provided numerical data and reported higher bone mineral content in the intervention group: WMD 12.0 (95% CI 6.3 to 17.7) mg/cm. Modanlou 1986, Gross 1987 (1), and Gross 1987 (2) detected no statistically significant differences between control and treatment groups but did not report numerical data for inclusion in meta-analyses.

Measures of metabolic health for long-term follow-up

None of the trials reported these measures.

Subgroup analyses

Very preterm or VLBW infants

Meta-analyses of data from trials that restricted participation to very preterm or VLBW infants showed no differences in the meta-analyses of all trial data (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13).

Fortifcation of donor breast milk

One trial used donor milk exclusively (Adhisivam 2019). Seven trials supplemented mother's own milk with donor milk (Gross 1987 (1); Gross 1987 (2); Polberger 1989; Porcelli 1992; Nicholl 1999; Faerk 2000; Mukhopadhyay 2007). Outcome data for infants fed with donor breast milk exclusively were not available to include in subgroup meta-analyses with Adhisivam 2019.

Trials using fortifier extracted from human milk (rather than cow's milk-based fortifiers)

All trials included in this review used cow's milk-based fortifiers.

Trials using infant formula as the multi-nutrient fortifier

Gross 1987 (2) (for a subset of the intervention group); Zuckerman 1994; El Sakka 2016; and Gupta 2018 used preterm infant formula powder to fortify breast milk.

Growth parameters (Analysis 1.1; Analysis 1.2; Analysis 1.3). Meta-analysis of date from Gross 1987 (2) and Gupta 2018 showed pooled effects consistent with the overall meta-analyses (Figure 3; Figure 4; Figure 5).

Length of hospital stay (Analysis 1.9). Meta-analysis of date from Zuckerman 1994; El Sakka 2016; and Gupta 2018 showed pooled effects consistent with the overall meta-analysis.

Necrotising enterocolitis (Analysis 1.11). Meta-analysis of date from Zuckerman 1994 and Gupta 2018 showed pooled effects consistent with the overall meta-analysis.

Serum level of ALP (Analysis 1.12). Analysis of data from Zuckerman 1994 showed an effect consistent with the overall meta-analysis.

Trials conducted in low- and middle-income countries

Eight trials were conducted in middle-income countries: Pettifor 1989 and Zuckerman 1994 in South Africa (upper middle-income country), El Sakka 2016 in Egypt (lower middle-income country), Einloft 2015 in Brazil (upper middle-income country), and Mukhopadhyay 2007; Gathwala 2012; Gupta 2018; and Adhisivam 2019 in India (lower middle-income country). Meta-analyses showed no significant differences from the meta-analyses of all trials together (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13).

DISCUSSION

Summary of main results

Evidence from 18 randomised controlled trials shows that multi-nutrient fortification results in modest increases in in-hospital rates of weight gain, length gain, and head growth for preterm infants. Few data are available for growth and developmental outcomes assessed beyond infancy, and these show no effects of fortification. None of the trials has reported data related to possible longer-term "programmed" metabolic or physiological consequences of multi-nutrient supplementation in early infancy.

Meta-analysis of data from trials that included a control group without bone mineral supplementation showed that multi-nutrient fortification reduces serum alkaline phosphatase (ALP) levels but provided limited evidence of effects on other measures of bone mineralisation or health. This review found no consistent evidence of other benefits or harms of multi-nutrient fortification, including no data to suggest that fortification increases the risk of feed intolerance or necrotising enterocolitis in preterm infants.

Overall completeness and applicability of evidence

We recommend cautious interpretation and application of these findings. Although meta-analyses indicate that multi-nutrient fortification increases rates of growth, typical effect sizes are small.

Over the course of four weeks, multi-nutrient fortification for a very preterm infant weighing 1 kg at birth would result in an extra 50 g of weight gain, 4 mm of length gain, and 2 mm of head circumference gain. The clinical importance of these effects on in-hospital growth rates is unclear, and uncertainty remains about the long-term impact on growth or development. Similarly, although multi-nutrient fortification that includes minerals (versus human breast milk without added minerals) reduces the serum ALP level, this is an insensitive measure of bone mineralisation or health (Tinnion 2012). In current clinical practice, mineral supplements (mainly phosphate) are available for infants at high risk of, or with biochemical or other features of, metabolic bone disease.

Meta-analyses of growth outcomes showed heterogeneity that was not explained by major differences in trial design or conduct. Participants in these trials were similar (mostly stable very low birth weight (VLBW) infants). Although we noted some variation in the types of fortifier used, the overall target level of fortification and the duration of administration were similar. Most trials aimed to provide extra protein and non-protein energy by adding a powdered, commercially available, multi-nutrient fortifier to breast milk to attain about 80 kcal/100 mL and about 2.0 to 2.6 g of protein/100 mL (plus proportionate supplements of minerals, vitamins, and trace elements). This approach aims to maintain optimal protein-to-energy ratios to ensure that the protein contributed to growth and was not catabolised as a fuel source (Kashyap 1994). These total levels of protein and energy, however, are at the lower bounds of currently recommended intakes needed to match intrauterine accretion (based on receiving about 150 mL/kg/d of milk), and this is a possible explanation for the modest impact of the intervention on growth parameters.

A major limitation of this review is that most included trials were undertaken at healthcare facilities in high-income countries, and few were conducted in community settings or in middle- or low-income countries. Reported evidence therefore may be of limited use to inform care practice in the resource-limited settings where most preterm and low birth weight infants are cared for globally (Imdad 2013).

Quality of the evidence

We assessed the certainty of evidence as low or moderate for most outcomes (Summary of findings 1). Included trials were generally small and had methodological quality weaknesses, including inadequate measures to conceal random allocation and incomplete follow-up assessment during the intervention period. Masking of clinicians, parents, and caregivers was not possible given the nature of the intervention, but this is not likely to be a major source of bias in growth assessments. Knowledge of the intervention group may have affected caregivers' or mothers' perceptions and views of feeding, and it may have influenced decisions on whether any formula should be given as a supplement to (or instead of) breast milk. These trials did not examine whether multi-nutrient fortification affected the mother's commitment to establish breastfeeding, or whether differences were noted in the proportion of infants receiving any breast milk at the end of the intervention period.

Potential biases in the review process

Our main concern with the review process is the possibility that findings may be subject to publication and other reporting biases. We attempted to minimise this threat by screening the reference lists of included trials and related reviews and searching the proceedings of major international perinatal conferences to identify trial reports that are not (or are not yet) published in full form in academic journals. The meta-analyses that we performed did not contain sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or reporting bias.

Agreements and disagreements with other studies or reviews

These findings are broadly consistent with those of another Cochrane Review, which showed that preterm infants who received nutrient-enriched formula (similar energy and protein levels to multi-nutrient fortified human breast milk) versus standard formula (similar energy and protein levels to unfortified human breast milk) had higher in-hospital rates of weight gain (mean difference (MD) 2.43 g/kg/d, 95% confidence interval (CI) 1.60 to 3.26), length gain (MD 0.02 cm/week, 95% CI -0.07 to 0.11), and head circumference growth (MD 0.1 cm/week, 95% CI 0.02 to 0.19) (Walsh 2019).

AUTHORS' CONCLUSIONS

Implications for practice

Multi-nutrient fortification of human milk is associated with small, short-term increases in weight gain and in linear and head growth. There is no evidence to suggest that these short-term gains lead to any long-term effects on growth or development. Investigators reported no increase in adverse effects among infants who received multi-nutrient fortifiers, although the total number of infants studied was small and the data that could be abstracted from published studies were limited.

Implications for research

Given the potential for multi-nutrient fortification of breast milk to affect important outcomes in preterm infants, this intervention merits further assessment. As this practice is already widely established and accepted as a standard of care in many neonatal units, it is important for researchers to determine whether mothers and clinicians would support a trial of this intervention. All trials should be powered to detect potentially important effects on growth rates, as well as potential adverse consequences, during infancy and beyond. Trials should attempt to ensure that caregivers and assessors are blind to the intervention. Although this goal is more easily achievable for longer-term assessments, it is also important for ascertainment of adverse events, such as feeding intolerance and necrotising enterocolitis, when the threshold for investigation or diagnosis may be affected by knowledge of the intervention. We have identified one such planned trial (Mills 2015).

New research areas

Most commercially available fortifiers contain protein, carbohydrate, calcium, phosphate, other minerals (zinc, manganese, magnesium, and copper), vitamins, and electrolytes. Investigators have not evaluated the benefits of many of these individual components in a controlled manner. Future research could compare different proprietary preparations to evaluate both short-term and long-term outcomes and adverse effects, while searching for the "optimal" composition of fortifiers. Investigators could examine the effects of targeted or adjustable fortification to

determine whether human milk-based fortifier provides any cost-effective advantages over cow's milk-based fortifier.

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As a Cochrane Neonatal Associate Editor, XX has peer reviewed and offered feedback for this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adhisivam 2019

Study characteristics	
Methods	Randomised controlled trial
Participants	80 "healthy" preterm infants (average gestational age at birth = 32 weeks, average birth weight 1400 g) Exclusion criteria: major congenital anomalies, surgical problems of the gastrointestinal tract, birth asphyxia, and early-onset sepsis Setting: Department of Neonatology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
Interventions	Intervention (N = 40): fortified donor human milk (4 g of commercially available powdered fortifier per 100 mL of milk, resulting in extra 2 g of protein and 13.3 kcal per 100 mL) Control (N = 40): donor human milk without fortifier
Outcomes	• Necrotising enterocolitis • Rate of weight gain and head circumference growth • Duration of hospital stay
Notes	All participants received multi-vitamin and iron supplements Human milk was enriched with a fortifier when infants reached an intake volume of 100 mL/kg/d

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Study authors report use of "computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Study authors report use of "opaque sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was described as "unblinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was described as "unblinded"

Adhisivam 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised infants have been included for intention-to-treat analyses

Bhat 2003

Study characteristics	
Methods	Randomised controlled trial
Participants	100 VLBW infants Exclusion criterion: need for prolonged mechanical ventilation Setting: Special Care Baby Unit, Khoula Hospital, Muscat, Oman
Interventions	Intervention (N = 50): fortified human milk (4 g of powdered fortifier to achieve 81 kcal, 2.4 g protein, and 9.0 g carbohydrates per 100 mL of milk) Control (N = 50): human milk only If amounts were insufficient, human milk was supplemented with formula up to a maximum of 15% of energy for 2 days. Babies who required supplementation beyond this were excluded from the study
Outcomes	• Weight gain • Markers of nutritional and bone mineral status • Adverse events including necrotising enterocolitis
Notes	Human milk was enriched with a fortifier when infants received 140 mL/kg/d

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	No details were reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as "double-blind", but it was not specified who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was described as "double-blind", but it was not specified who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up were reported. Lack of attrition bias was assumed

Einloft 2015

Study characteristics	
Methods	Randomised controlled trial
Participants	83 VLBW infants (average gestational age at birth = 29.7 weeks, average birth weight 1160 g) Exclusion criteria: acute or chronic disease, including congenital malformations, heart or neurologic disease, or inborn errors of metabolism; and newborns undergoing surgery or using diuretics and corticosteroids • *NB. Randomised participants were excluded retrospectively if they (a) received parenteral nutrition for longer than 10 days or used mechanical ventilation, (b) received continuous positive airway pressure or supplemental oxygen, (c) developed any serious condition such as necrotising enterocolitis or sepsis, (d) did not undergo densitometry at discharge, or (e) did not reach a minimum volume of 50% of human milk during the study period (i.e. fed premature infant formula)* Setting: Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil
Interventions	Intervention (N = 41): fortified maternal milk (5 g of commercially available powdered fortifier per 100 mL of milk, resulting in extra 1 g of protein and 17 kcal per 100 mL) Control (N = 42): maternal milk without fortifier
Outcomes	• Bone mineral content (DEXA scan) when infant weight = 2000 g • Rate of weight gain, length gain, and head circumference growth • Duration of hospital stay
Notes	All participants received multi-vitamin and iron supplements enterally (*but not minerals*) Funded by Nestle

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	High risk	Report states that participants were "randomly assigned", but "no allocation concealment" was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was described as "unblinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was described as "unblinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	Forty-five infants (22 in the supplemented group and 23 in the unsupplemented group) were excluded from the study after randomisation. Reasons for exclusion were reported: "*After hospital discharge, retrospective exclusions resulted in a total sample of 38 newborns who were included in the analysis (supplemented group, N = 19; control group, N = 19)*"

El Sakka 2016

Study characteristics	
Methods	Randomised controlled trial
Participants	59 preterm VLBW infants (average gestational age at birth = 32 weeks, average birth weight 1292 g) Exclusion criteria: congenital abnormalities, intolerance to enteral feeds, hyperbilirubinaemia requiring phototherapy, hypoglycaemia, hyponatraemia, or respiratory illness necessitating any kind of assisted ventilation; or mothers with contraindication to breastfeeding Setting: Department of Neonatology, Faculty of Medicine, AinShams University, Cairo, Egypt
Interventions	Intervention (N = 29): maternal milk fortified with "post-discharge formula" powder (to achieve estimated average 83 kcal, 1.45 g protein, and 8.7 g carbohydrates per 100 mL of milk) Control (N = 30): maternal milk without fortifier
Outcomes	• Feed intolerance (necrotising enterocolitis not reported) • Rate of weight gain and head circumference growth • Duration of hospital stay
Notes	All participants received vitamin D and iron supplements Human milk was enriched with post-discharge formula powder when infants reached an intake volume of 100 mL/kg/d and continued until infant weight = 1800 g

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly categorized", but the method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	No details were reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was likely to be unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was likely to be unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Post-randomisation exclusion of 9/59 (15%) participants

Faerk 2000

Study characteristics	
Methods	Randomised controlled trial
Participants	103 very preterm infants

Faerk 2000 *(Continued)*

	Exclusion criterion: major congenital anomaly Setting: NICUs, Rigshospitalet and Hvidovre Hospital, Copenhagen, Denmark
Interventions	Intervention (N = 51): human milk (maternal or donor) supplemented with 0.4 g protein, 1.4 g carbohydrate, 35 mg calcium, and 17 mg phosphorus per 100 mL (Milupa Eoprotin) Control (N = 52): maternal or donor milk supplemented with 10 mg phosphate per 100 mL
Outcomes	• Weight, length, and head circumference at term • Measures of bone mineralisation (DEXA scan) • Necrotising enterocolitis
Notes	Target intake of 200 mL/kg/d All infants received vitamin D 800 IU per day Intervention ceased when breastfed or at 36 weeks' postmenstrual age

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is described as "double-blind", but it is not specified who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is described as "double-blind", but it is not specified who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	103 infants were randomised, but outcome data were reported for only 76 (74%) because of loss to follow-up or technical problems with DEXA scans. Further information about outcomes was not available from investigators

Gathwala 2012

Study characteristics

Methods	Randomised controlled trial
Participants	67 consecutive preterm infants of birth weight < 1800 g Eligibility criteria: healthy preterm infants, appropriate for gestational age, no birth asphyxia, enterally fed with breast milk by 14 days of life, no congenital malformations, no ventilatory support previous 7 days, no diuretic or steroid therapy Setting: Neonatology Unit, Department of Paediatrics, Pt. B.D. Sharma PGIMS, Rohtak, India
Interventions	Intervention (N = 34): breast milk fortified with Lactodex Human Milk Fortifier (to achieve 80 kcal, 9.4 g carbohydrate, and 2.2 g protein per 100 mL, plus minerals and electrolytes)

Gathwala 2012 *(Continued)*

	Control (N = 33): unfortified breast milk Infants were excluded from the study if they needed more than 25% of their daily requirements to be provided by formula or other milk
Outcomes	• Time to regain birth weight • Time to reach 2200 g • Duration of hospital stay • Biochemical markers of nutritional status (including serum ALP)
Notes	Incidence of feed intolerance or necrotising enterocolitis is not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a random numbers table
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment are not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four babies in the intervention group and 3 in the control group were excluded post randomisation, as their need for additional milk exceeded 25%. These infants were not included in intention-to-treat analyses

Gross 1987 (1)

Study characteristics

Methods	Randomised controlled trial (2-phase trial, referred to as Gross 1987 (1) and Gross 1987 (2))
Participants	20 infants with birth weight < 1600 g Eligibility criteria: birth weight appropriate for gestational age, free from congenital anomaly or major disease, breathing room air, ability to begin enteral feeding within first week after birth Setting: Duke University Medical Center, Durham, North Carolina, USA
Interventions	Intervention (N = 10): human milk mixed with preterm infant formula Similac Special Care (Ross Laboratories) containing 1.8 g protein per 100 mL, as well as carbohydrate Control (N = 10): human milk with no supplementation Feeding of human milk supplemented with formula commenced after 1 week of enteral feeds of unfortified human milk. All infants received intravenous dextrose and electrolytes until day 5 of feeding. All infants received supplemental vitamins with their milk from day 8 of feeding
Outcomes	• In-hospital growth parameters

Gross 1987 (1) *(Continued)*

- Growth at 44 weeks' postmenstrual age
- Bone mineral content and biochemical indices of bone metabolism

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation are not reported. Report states that infants were "assigned randomly" to receive fortified or unfortified breast milk
Allocation concealment (selection bias)	Unclear risk	Report states that "sealed envelopes" were used, but it is unclear whether these were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not reported whether personnel were blinded (participant blinding is irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up are reported. Lack of attrition bias is assumed

Gross 1987 (2)

Study characteristics

Methods	Randomised controlled trial (2-phase trial, referred to as Gross 1987 (1) and Gross 1987 (2))
Participants	30 infants with birth weight < 1600 g Eligibility criteria: birth weight appropriate for gestational age, free from congenital anomaly or major disease, breathing room air, ability to begin enteral feeding within first week after birth Setting: Boston Perinatal Center, Boston, Massachusetts, USA
Interventions	Intervention 1 (N = 11): human milk mixed with preterm infant formula Similac Special Care (Ross Laboratories) containing 1.8 g protein per 100 mL, as well as carbohydrate (as above for Gross 1987 (1)) Intervention 2 (N = 10): human milk mixed with powdered breast milk fortifier Control (N = 9): human milk with no supplementation Fortification with the powdered fortifier was introduced after 2 weeks of enteral feeds of unfortified human milk. All infants received intravenous dextrose and electrolytes until day 5 of feeding. All infants received supplemental vitamins with their milk from day 8 of feeding. For this review, participants from the 2 intervention groups were taken together as infants receiving fortification
Outcomes	• In-hospital growth parameters • Growth at 44 weeks' postmenstrual age • Bone mineral content and biochemical indices of bone metabolism

Gross 1987 (2) *(Continued)*

Notes	The full composition of powdered fortifier is not reported in the paper. We deemed it appropriate for inclusion as powdered formula appeared to include protein and energy, as required by our inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of sequence generation are not reported. Report states that infants were "assigned randomly" to receive fortified or unfortified breast milk
Allocation concealment (selection bias)	Unclear risk	Report states that "sealed envelopes" were used, but it is unclear whether these were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four infants (2 in intervention group 1, and 2 in intervention group 2) did not complete the study because of feed intolerance. Results of growth outcomes for these infants are not presented

Gupta 2018

Study characteristics

Methods	Randomised controlled trial
Participants	163 VLBW infants Eligibility criteria: major congenital malformation, necrotising enterocolitis stage 2 or 3, not reaching full volume feeds by day 21 of life Setting: Department of Neonatology, Christian Medical College Vellore Tamil Nadu, India
Interventions	Intervention 1 (N = 82): maternal milk mixed with infant formula powder (Simyl LBW, FDC Ltd, India) to achieve 2 g protein and 88 kcal per 100 mL Control (N = 81): human milk with no supplementation Fortification with the powdered formula was continued until infant weight = 1800 g
Outcomes	• Feed intolerance • Necrotising enterocolitis • Rate of weight and length gain and head circumference growth • Duration of hospital stay
Notes	All participants received multi-vitamin, calcium, and iron supplements Study was supported by institutional research grant from Christian Medical College, Vellore

Risk of bias

Gupta 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Statistician-generated" sequence
Allocation concealment (selection bias)	Low risk	Serially numbered, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete cohort analysis (by intention-to-treat)

Lucas 1996

Study characteristics	
Methods	Randomised controlled trial
Participants	275 preterm infants with birth weight < 1850 g Eligibility criteria: no major congenital abnormalities, resident in UK, mother agreed to provide breast milk Setting: 2 centres in Cambridge and Norwich, UK
Interventions	Intervention (N = 137): maternal milk supplemented with (per 100 mL) 0.7 g protein (bovine), 2.73 g carbohydrate, 0.05 g fat, 90 mg calcium, and 45 mg phosphate, as well as electrolytes (Enfamil, Mead Johnson) Control (N = 138): maternal milk supplemented with 15 mg/100 mL phosphate Enteral intake 180 mL/kg/d Intervention ceased at discharge, or when weight reached 2000 g All infants received vitamins (including vitamin D 260 IU/100 mL) Infants whose mothers could not provide sufficient milk were supplemented with a preterm formula and were not excluded from the analysis
Outcomes	• In-hospital growth rates • Growth to 9 and 18 months • Neurodevelopmental outcomes at 9 and 18 months • Serum indices of bone metabolism • Necrotising enterocolitis
Notes	Funded by Mead Johnson

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Lucas 1996 *(Continued)*

Random sequence generation (selection bias)	Low risk	Use of permuted blocks of randomised length
Allocation concealment (selection bias)	Low risk	Use of sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded (except for assessment of neurodevelopmental outcomes)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up are reported. Lack of attrition bias is assumed

Modanlou 1986

Study characteristics	
Methods	Randomised controlled trial
Participants	39 infants of birth weight between 1000 and 1500 g Eligibility criteria: birth weight appropriate for gestational age, no ventilatory assistance after 7 days, no supplemental oxygen after 10 days, fewer than 3 days of diuretic therapy, enteral feeding by 14 days after birth Setting: Miller Children's Hospital of Long Beach, California, USA
Interventions	Intervention (N = 20): mother's own milk plus fortifier (to provide supplemental 0.7 g protein, 2.7 g carbohydrate, "trace" fat, 60 mg calcium, and 33 mg phosphate per 100 mL of breast milk) Control (N = 19): mother's own milk Formula and human milk were diluted initially and the fortifier was added gradually to milk for infants in the intervention group to reach target calorific density over 7 days (approximately) in all groups. Milk was generally provided by intermittent bolus gavage until nipple feedings were tolerated. Infants received standard infant formula if their mother's milk was unavailable for "an occasional feeding" (up to a maximum of 10% of feedings per week)
Outcomes	• Growth rates (weight, length, head circumference) • Feeding intolerance and necrotising enterocolitis • Biochemical status • Bone mineral content
Notes	Intervention ceased at discharge, or when weight reached 1800 g
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Modanlou 1986 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Report states that sealed envelopes were used. It is not reported whether these were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	19 infants left the study after randomisation because of "insufficient maternal milk supply", and another 2 infants were withdrawn because of suspected NEC. Outcome data for inclusion in intention-to-treat analyses were not available for these infants

Mukhopadhyay 2007

Study characteristics	
Methods	Randomised controlled trial
Participants	166 VLBW infants (and gestational age < 35 weeks at birth) Eligibility criteria: feed volume of 150 mL/kg/d, feeds consisting of at least 80% breast milk, no congenital malformations nor gastrointestinal abnormalities Setting: PGIMER, Chandigarh, India
Interventions	Intervention (N = 85): breast milk fortified with Lactodex Human Milk Fortifier (2 g sachet per 50 mL of milk: 0.2 g protein, 1.2 g carbohydrate, and 6.5 kcal energy) Control (N = 81): breast milk with added vitamins and minerals
Outcomes	• Growth rates (weight, length, head circumference) • Biochemical parameters • Length of hospital stay • Feeding intolerance and necrotising enterocolitis
Notes	Fortification was stopped once babies reached a weight of 2000 g or were fully breastfed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Details not reported

Mukhopadhyay 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up are reported. Lack of attrition bias is assumed

Nicholl 1999

Study characteristics	
Methods	Randomised controlled trial
Participants	23 VLBW infants receiving enteral feeds of at least 150 mL/kg/d Eligibility criteria: no fluid restriction, no diuretics, no postnatal systemic steroid use, no significant congenital abnormality Setting: neonatal intensive care unit, King's College Hospital, London, UK
Interventions	Intervention (N = 13): maternal (or pasteurised pooled donor milk) supplemented (per 100 mL) with 0.7 g protein, 2.0 g carbohydrate, 30 mg calcium, 40 mg phosphorus, trace minerals, and vitamins Control (N = 10): unsupplemented maternal or donor milk Intervention ceased when infants no longer required nasogastric feeds
Outcomes	• In-hospital growth parameters • Indices of bone metabolism
Notes	Intervention ceased when infants no longer required nasogastric feeds One infant whose mother declined fortifier was included in results of non-fortified infants, and 1 baby whose mother preferred the addition of fortifier was included in results of the intervention group

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomised", but method of sequence generation is not described
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias)	High risk	Unblinded

Nicholl 1999 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up are reported. Lack of attrition bias is assumed

Pettifor 1989

Study characteristics	
Methods	Randomised controlled trial
Participants	100 consecutive infants weighing between 1000 and 1500 g at birth Eligibility criteria: no major congenital abnormalities or metabolic disturbances, no requirement for ventilation at the point of entry into the study (day 4 after birth), free from serious infection, receiving at least 45 mL/kg/d of gavage feedings (expressed breast milk) at the beginning of the study Setting: Baragwanath Hospital, Bertsham, South Africa
Interventions	Intervention (N = 53): mother's own milk supplemented with (per 100 mL) 0.05 g protein, 1.1 g carbohydrate, 0.26 g fat, 72.3 mg calcium, and 34 mg phosphate, along with electrolytes and vitamins (HMF, Ross Laboratories) Control (N = 47): mother's own milk Feeds were titrated as tolerated up to 200 mL/kg/d. Feeds were delivered by nasogastric tube until infants weighed 1600 g. At this point, bottle feeding was introduced gradually. Infants were removed from the study if their mother could not supply sufficient breast milk
Outcomes	• Weight gain • Serum calcium, phosphorus, alkaline phosphatase, and albumin levels • Bone mineral homeostasis • Necrotising enterocolitis (data obtained from trial investigators)
Notes	41 infants left the study after randomisation for various reasons (insufficient maternal milk supply, death, reduced enteral intake for > 72 hours, incomplete data). Data for these infants were not included in intention-to-treat analyses of growth outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias)	Unclear risk	It is not reported whether outcome assessors were blinded

Pettifor 1989 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	41 (of 100) infants left the study after randomisation for various reasons (insufficient maternal milk supply, death, reduced enteral intake for > 72 hours, incomplete data). These infants were not included in intention-to-treat analyses of growth outcomes

Polberger 1989

Study characteristics	
Methods	Randomised controlled trial
Participants	34 VLBW infants Eligibility criteria: birth weight appropriate for gestational age, tolerance of complete enteral feeding (170 mL/kg/d), no obvious disease or major malformations, no supplemental oxygen therapy Setting: 2 neonatal units in Lund and Malmö, Sweden
Interventions	Intervention (N = 7): maternal or donor milk supplemented with (per 100 mL) 1.0 g human milk protein and 1.0 g human milk fat Control 1 (N = 7): maternal or donor milk with no fortification Feeds of 170 mL/kg/d were given throughout the study. When mother's own milk was insufficient, mature human milk from a milk bank was used. All infants, regardless of group allocation, received enteral supplementation with vitamin E, folic acid, a multi-vitamin preparation, and additional vitamin D. They also received one-off administration of calcium and phosphate, and from 4 weeks of age, elemental iron was given
Outcomes	• Growth parameters
Notes	Six infants left the study after randomisation for various reasons (apnoea, intolerance to the fixed feed volume, need for intravenous therapy). These infants were not included in intention-to-treat analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomly assigned", but method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Report states that "closed envelopes" were used, but it is not specified whether these were sequentially numbered, opaque, and sealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double-blind", but it is not specified who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double-blind", but it is not specified who was blinded
Incomplete outcome data (attrition bias)	High risk	Several (up to 6, but exact number unclear) infants were excluded from the study after randomisation; intention-to-treat analyses were not reported

Polberger 1989 *(Continued)*

All outcomes

Porcelli 1992

Study characteristics	
Methods	Randomised controlled trial
Participants	20 preterm infants with birth weight between 1110 and 2000 g Eligibility criteria: none reported Setting: Pediatric Hospital "V. Buzzi", Milano, Italy
Interventions	Intervention (N = 10): human milk fortified with FM85 Nestlè (including energy and protein) Control 1 (N =10): human milk with no fortification All infants received supplemental vitamin D
Outcomes	• Growth parameters • Metabolic parameters • Measures of bone mineralisation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Report states that infants were "randomised", but method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment are not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not reported whether personnel were blinded (participant blinding irrelevant in this context)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No details of infants lost to follow-up are reported. Lack of attrition bias is assumed

Wauben 1998

Study characteristics	
Methods	Randomised controlled trial

Wauben 1998 *(Continued)*

Participants	31 preterm infants of birth weight < 1800 g Eligibility criteria: older than 1 week of age (birth weight appropriate for gestational age), consumption of full oral feeds (enteral intake 160 mL/kg/d) for longer than 5 days, stable weight gain greater than 10 g/kg/d, no severe congenital malformations/chromosomal abnormalities, no gastrointestinal disease Setting: Neonatal Units of the Children's Hospitals of the Hamilton Health Sciences Corporation and St Joseph's Hospitals, Hamilton, Ontario, Canada
Interventions	Intervention (N = 15): maternal milk fortified with (per 100 mL) 0.37 g human milk protein, 3.47 g carbohydrate, 61 mg calcium, 44 mg phosphorus, electrolytes and other minerals, and vitamins (including vitamin D 472 IU/d) (Wyeth-Ayerst, Toronto, Ontario, Canada) (fortification commenced when maternal milk contributed > 80% of infant's enteral intake) Control (N = 16): maternal milk supplemented with calcium glycerophosphate
Outcomes	• Short-term growth • Biochemical indices of bone metabolism • Bone mineral content
Notes	Supplementation in both groups was increased gradually until a target amount was reached. Intervention ceased at discharge or at 38 weeks' postmenstrual age, whichever occurred later Infants in the control arm were significantly lighter at birth and were significantly lighter and shorter at study entry than infants in the group receiving HMF Nutrient intakes were measured: mean fluid intakes were significantly greater in the control group (177 vs 164 mL/kg/d)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment are not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Six infants (3 in each group) were excluded from the study after randomisation. Details are reported, and no bias was apparent between groups. Intention-to-treat analyses of growth outcomes data are not reported

Zuckerman 1994

Study characteristics

Methods	Quasi-randomised controlled trial

Zuckerman 1994 *(Continued)*

Participants	56 infants with birth weight < 1200 g, older than 2 weeks of age Eligibility criteria: no congenital abnormalities, infections, nor disorders causing bone disease Setting: Baragwanath Hospital, Bertsham, South Africa
Interventions	Intervention (N = 29): maternal milk mixed in equal proportions with preterm infant formula (Alprem, Nestle) to yield supplements (per 100 mL) of fat, carbohydrate, and calcium 14.5 mg; phosphate 7 mg; and protein 0.6 g Control (N = 27): unsupplemented human milk
Outcomes	• In-hospital growth rates • Serum indices of bone metabolism • Radiographic changes in metabolic bone disease
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Infants were assigned to the 2 groups according to their hospital number (odd or even)
Allocation concealment (selection bias)	High risk	Infants were assigned to the 2 groups according to their hospital number (odd or even)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded (radiographers are reported to have been blinded)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three infants in the control group were excluded because of incorrect feeding

ALP: alkaline phosphatase.
DEXA: dual-energy X-ray absorptiometry.
NEC: necrotising enterocolitis.
NICU: neonatal intensive care unit.
VLBW: very low birth weight.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abrams 2014	Comparison of human milk-based vs cow's milk-based protein fortification
Arco 2002	Not an RCT
Arslanoglu 2009	Comparison of different fortification regimens, with no control group receiving unfortified milk

Study	Reason for exclusion
Atchley 2019	Fortification with protein only; comparison of diets with different energy:protein ratios
Biasini 2017	Not an RCT
Carey 1987	Fortification with protein only; no fortification with energy
Chan 2000	Comparison of different fortifiers, with no control group receiving unfortified milk
Greer 1988	Fortification with protein only; no fortification with energy
Hair 2014	Control group received fortified milk
Kashyap 1990	Fortification with protein only; no fortification with energy
Kim 2015	Comparison of different fortifiers (liquid vs powder), with no control group receiving unfortified milk
Miura 2009	Comparison of different fortifiers (MCT vs non-MCT enriched), with no control group receiving unfortified milk
Ramaswamy 2019	Not a randomised controlled trial (commentary on Gupta 2018)
Reali 2010	Literature review
Tarcan 2004	Not a randomised controlled trial

MCT: medium-chain triglyceride.
RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

Uthaya 2007

Methods	Randomised controlled trial
Participants	Infants born before 33 weeks' gestation, with blood urea level < 2.5 mmol/L
Interventions	"Breast milk fortifier" containing long-chain unsaturated fatty acids
Outcomes	Term body composition (adipose and lean tissue content)
Notes	Unpublished (brief abstract only) - further information sought from authors in October 2019 (not available)

Characteristics of ongoing studies *[ordered by study ID]*

Mills 2015

Study name	PREterM FOrmula Or Donor Breast Milk for Premature Babies (PREMFOOD)
Methods	Open, 3-arm randomised controlled feasibility trial

Mills 2015 *(Continued)*

Participants	Neonates at < 30 weeks' gestation; babies with conditions that preclude enteral feeding or are immediately life-limiting are ineligible
Interventions	Participants will be randomised to receive fortified donor breast milk (DBM), unfortified DBM, or preterm formula to make up any shortfall in maternal breast milk until 35 weeks' postmenstrual age, with a sample size of 22 in each group
Outcomes	Primary outcome measure: total body adiposity (measured as close as possible to the baby's due date, at an average age of 10 weeks (range 8 to 15 weeks))
Starting date	2015
Contact information	Prof. Neena Modi, Section of Neonatal Medicine, Imperial College London, London, UK; Department of Neonatal Medicine, Chelsea and Westminster Hospital, London, UK
Notes	Feasibility trial

DATA AND ANALYSES

Comparison 1. Fortified breast milk versus unfortified breast milk

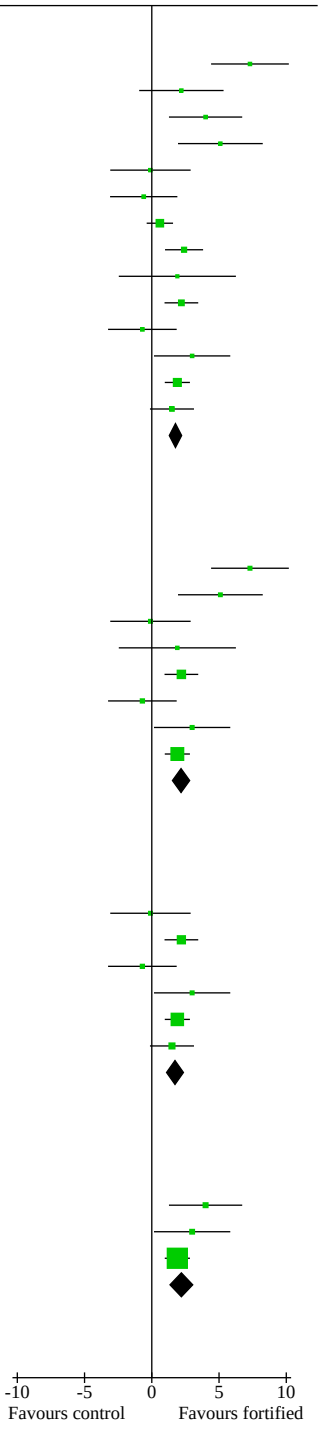
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Weight gain (g/kg/d)	14		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 All trials	14	951	Mean Difference (IV, Fixed, 95% CI)	1.76 [1.30, 2.22]
1.1.2 Trials recruiting only very preterm or VLBW infants	8	505	Mean Difference (IV, Fixed, 95% CI)	2.18 [1.54, 2.81]
1.1.3 Trials conducted in low- or middle-income countries	6	530	Mean Difference (IV, Fixed, 95% CI)	1.73 [1.10, 2.35]
1.1.4 Trials using preterm formula powder as fortifier	3	224	Mean Difference (IV, Fixed, 95% CI)	2.20 [1.36, 3.04]
1.2 Length gain (cm/week)	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 All trials	10	741	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.08, 0.15]
1.2.2 Trials recruiting only very preterm or VLBW infants	5	375	Mean Difference (IV, Fixed, 95% CI)	0.16 [0.11, 0.20]
1.2.3 Trials conducted in low- or middle-income countries	3	343	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.09, 0.19]
1.2.4 Trials using preterm formula powder as fortifier	2	174	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.01, 0.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Head growth (cm/week)	11		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 All trials	11	821	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.03, 0.08]
1.3.2 Trials recruiting only very preterm or VLBW infants	5	375	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.03, 0.11]
1.3.3 Trials conducted in low- or middle-income countries	4	423	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.01, 0.08]
1.3.4 Trials using preterm formula powder as fortifier	2	174	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.00, 0.11]
1.4 Weight at 12 to 18 months (kg)	2	270	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.31, 0.25]
1.5 Length at 12 to 18 months (cm)	2	270	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.98, 0.60]
1.6 Head circumference at 12 to 18 months (cm)	2	270	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.37, 0.18]
1.7 Mental development index at 18 months	1	245	Mean Difference (IV, Fixed, 95% CI)	2.20 [-3.35, 7.75]
1.8 Psychomotor development index at 18 months	1	245	Mean Difference (IV, Fixed, 95% CI)	2.40 [-1.90, 6.70]
1.9 Length of hospital stay (weeks)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.9.1 All trials	6	526	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.35, 0.21]
1.9.2 Trials recruiting only very preterm or VLBW infants	3	236	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.89, -0.08]
1.9.3 Trials conducted in low- or middle-income countries	4	316	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.55, 0.09]
1.9.4 Trials using preterm formula powder as fortifier	3	251	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.85, -0.05]
1.10 Feed intolerance	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 All trials	7	453	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.65, 1.67]
1.10.2 Trials recruiting only very preterm or VLBW infants	4	372	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.55, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.3 Trials conducted in low- or middle-income countries	3	355	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.54, 1.47]
1.10.4 Trials using preterm formula powder as fortifier	3	228	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [0.79, 8.71]
1.11 Necrotising enterocolitis	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.11.1 All trials	13	1110	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.72, 2.63]
1.11.2 Trials recruiting only very preterm or VLBW infants	9	701	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.55, 2.99]
1.11.3 Trials conducted in low- or middle-income countries	6	552	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.36, 3.38]
1.11.4 Trials using preterm formula powder as fortifier	2	201	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.21, 10.76]
1.12 Serum ALP (IU/L): restricted to trials without mineral supplementation of the control group	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.12.1 All trials	6	363	Mean Difference (IV, Fixed, 95% CI)	-141.93 [-203.93, -79.92]
1.12.2 Trials recruiting only very preterm or VLBW infants	4	265	Mean Difference (IV, Fixed, 95% CI)	-132.03 [-198.09, -65.98]
1.12.3 Trials conducted in low- or middle-income countries	4	309	Mean Difference (IV, Fixed, 95% CI)	-119.66 [-185.54, -53.78]
1.12.4 Trials using preterm formula powder as fortifier	1	33	Mean Difference (IV, Fixed, 95% CI)	-261.00 [-539.14, 17.14]
1.13 Bone mineral content (mg/cm): restricted to trials without mineral supplementation of the control group	1	59	Mean Difference (IV, Fixed, 95% CI)	12.00 [6.28, 17.72]

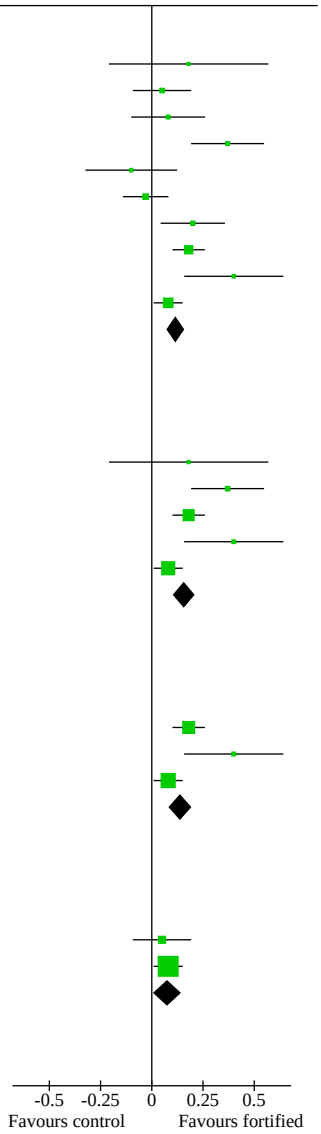
Analysis 1.1. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 1: Weight gain (g/kg/d)

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 All trials								
Modanlou 1986	26.7	3.4	8	19.4	2.7	10	2.5%	7.30 [4.41 , 10.19]
Gross 1987 (1)	19.9	2.5	10	17.7	4.4	10	2.1%	2.20 [-0.94 , 5.34]
Gross 1987 (2)	21.5	3.5	17	17.5	3.3	9	2.8%	4.00 [1.28 , 6.72]
Polberger 1989	20.4	2.8	7	15.3	3.2	7	2.1%	5.10 [1.95 , 8.25]
Pettifor 1989	16.7	5	29	16.8	6.4	28	2.4%	-0.10 [-3.09 , 2.89]
Porcelli 1992	11.4	2.7	10	12	3	10	3.4%	-0.60 [-3.10 , 1.90]
Lucas 1996	15.6	4.7	137	15	3.5	138	21.9%	0.60 [-0.38 , 1.58]
Wauben 1998	16.6	1.6	12	14.2	2	13	10.5%	2.40 [0.99 , 3.81]
Nicholl 1999	15.1	3.3	13	13.2	6.4	10	1.1%	1.90 [-2.45 , 6.25]
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	13.4%	2.20 [0.95 , 3.45]
Einloft 2015	19.2	4.3	19	19.9	3.7	19	3.2%	-0.70 [-3.25 , 1.85]
El Sakka 2016	16.8	5.5	25	13.8	4.7	25	2.6%	3.00 [0.16 , 5.84]
Gupta 2018	18	2.9	75	16.1	2.9	73	24.1%	1.90 [0.97 , 2.83]
Adhisivam 2019	9.4	2.2	40	7.9	4.8	40	7.9%	1.50 [-0.14 , 3.14]
Subtotal (95% CI)			**484**			**467**	**100.0%**	**1.76 [1.30 , 2.22]**
Heterogeneity: Chi² = 37.16, df = 13 (P = 0.0004); I² = 65%								
Test for overall effect: Z = 7.52 (P < 0.00001)								
1.1.2 Trials recruiting only very preterm or VLBW infants								
Modanlou 1986	26.7	3.4	8	19.4	2.7	10	4.9%	7.30 [4.41 , 10.19]
Polberger 1989	20.4	2.8	7	15.3	3.2	7	4.1%	5.10 [1.95 , 8.25]
Pettifor 1989	16.7	5	29	16.8	6.4	28	4.6%	-0.10 [-3.09 , 2.89]
Nicholl 1999	15.1	3.3	13	13.2	6.4	10	2.2%	1.90 [-2.45 , 6.25]
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	26.1%	2.20 [0.95 , 3.45]
Einloft 2015	19.2	4.3	19	19.9	3.7	19	6.3%	-0.70 [-3.25 , 1.85]
El Sakka 2016	16.8	5.5	25	13.8	4.7	25	5.1%	3.00 [0.16 , 5.84]
Gupta 2018	18	2.9	75	16.1	2.9	73	46.8%	1.90 [0.97 , 2.83]
Subtotal (95% CI)			**258**			**247**	**100.0%**	**2.18 [1.54 , 2.81]**
Heterogeneity: Chi² = 23.18, df = 7 (P = 0.002); I² = 70%								
Test for overall effect: Z = 6.67 (P < 0.00001)								
1.1.3 Trials conducted in low- or middle-income countries								
Pettifor 1989	16.7	5	29	16.8	6.4	28	4.4%	-0.10 [-3.09 , 2.89]
Mukhopadhyay 2007	15.1	4	82	12.9	4	75	25.0%	2.20 [0.95 , 3.45]
Einloft 2015	19.2	4.3	19	19.9	3.7	19	6.0%	-0.70 [-3.25 , 1.85]
El Sakka 2016	16.8	5.5	25	13.8	4.7	25	4.9%	3.00 [0.16 , 5.84]
Gupta 2018	18	2.9	75	16.1	2.9	73	45.0%	1.90 [0.97 , 2.83]
Adhisivam 2019	9.4	2.2	40	7.9	4.8	40	14.7%	1.50 [-0.14 , 3.14]
Subtotal (95% CI)			**270**			**260**	**100.0%**	**1.73 [1.10 , 2.35]**
Heterogeneity: Chi² = 6.44, df = 5 (P = 0.27); I² = 22%								
Test for overall effect: Z = 5.40 (P < 0.00001)								
1.1.4 Trials using preterm formula powder as fortifier								
Gross 1987 (2)	21.5	3.5	17	17.5	3.3	9	9.6%	4.00 [1.28 , 6.72]
El Sakka 2016	16.8	5.5	25	13.8	4.7	25	8.9%	3.00 [0.16 , 5.84]
Gupta 2018	18	2.9	75	16.1	2.9	73	81.5%	1.90 [0.97 , 2.83]
Subtotal (95% CI)			**117**			**107**	**100.0%**	**2.20 [1.36 , 3.04]**
Heterogeneity: Chi² = 2.38, df = 2 (P = 0.30); I² = 16%								
Test for overall effect: Z = 5.11 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.85, df = 3 (P = 0.60), I² = 0%								



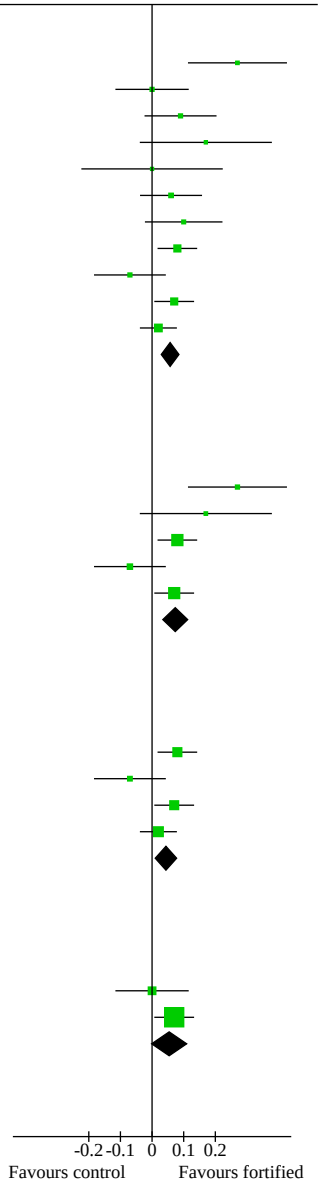
Analysis 1.2. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 2: Length gain (cm/week)

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 All trials								
Modanlou 1986	0.99	0.4	8	0.81	0.44	10	1.0%	0.18 [-0.21 , 0.57]
Gross 1987 (2)	0.84	0.25	17	0.79	0.12	9	7.8%	0.05 [-0.09 , 0.19]
Gross 1987 (1)	0.89	0.19	10	0.81	0.22	10	4.9%	0.08 [-0.10 , 0.26]
Polberger 1989	1.2	0.17	7	0.83	0.17	7	5.0%	0.37 [0.19 , 0.55]
Porcelli 1992	0.6	0.2	10	0.7	0.3	10	3.2%	-0.10 [-0.32 , 0.12]
Lucas 1996	0.93	0.47	137	0.96	0.47	138	12.8%	-0.03 [-0.14 , 0.08]
Wauben 1998	1.1	0.2	12	0.9	0.2	13	6.4%	0.20 [0.04 , 0.36]
Mukhopadhyay 2007	1.04	0.3	82	0.86	0.2	75	25.1%	0.18 [0.10 , 0.26]
Einloft 2015	1.2	0.5	19	0.8	0.2	19	2.7%	0.40 [0.16 , 0.64]
Gupta 2018	1.04	0.21	75	0.96	0.23	73	31.2%	0.08 [0.01 , 0.15]
Subtotal (95% CI)			**377**			**364**	**100.0%**	**0.11 [0.08 , 0.15]**
Heterogeneity: Chi² = 29.00, df = 9 (P = 0.0006); I² = 69%								
Test for overall effect: Z = 5.67 (P < 0.00001)								
1.2.2 Trials recruiting only very preterm or VLBW infants								
Modanlou 1986	0.99	0.4	8	0.81	0.44	10	1.6%	0.18 [-0.21 , 0.57]
Polberger 1989	1.2	0.17	7	0.83	0.17	7	7.6%	0.37 [0.19 , 0.55]
Mukhopadhyay 2007	1.04	0.3	82	0.86	0.2	75	38.6%	0.18 [0.10 , 0.26]
Einloft 2015	1.2	0.5	19	0.8	0.2	19	4.1%	0.40 [0.16 , 0.64]
Gupta 2018	1.04	0.21	75	0.96	0.23	73	48.0%	0.08 [0.01 , 0.15]
Subtotal (95% CI)			**191**			**184**	**100.0%**	**0.16 [0.11 , 0.20]**
Heterogeneity: Chi² = 14.21, df = 4 (P = 0.007); I² = 72%								
Test for overall effect: Z = 6.20 (P < 0.00001)								
1.2.3 Trials conducted in low- or middle-income countries								
Mukhopadhyay 2007	1.04	0.3	82	0.86	0.2	75	42.6%	0.18 [0.10 , 0.26]
Einloft 2015	1.2	0.5	19	0.8	0.2	19	4.5%	0.40 [0.16 , 0.64]
Gupta 2018	1.04	0.21	75	0.96	0.23	73	52.9%	0.08 [0.01 , 0.15]
Subtotal (95% CI)			**176**			**167**	**100.0%**	**0.14 [0.09 , 0.19]**
Heterogeneity: Chi² = 8.14, df = 2 (P = 0.02); I² = 75%								
Test for overall effect: Z = 5.20 (P < 0.00001)								
1.2.4 Trials using preterm formula powder as fortifier								
Gross 1987 (2)	0.84	0.25	17	0.79	0.12	9	19.9%	0.05 [-0.09 , 0.19]
Gupta 2018	1.04	0.21	75	0.96	0.23	73	80.1%	0.08 [0.01 , 0.15]
Subtotal (95% CI)			**92**			**82**	**100.0%**	**0.07 [0.01 , 0.14]**
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 2.28 (P = 0.02)								
Test for subgroup differences: Chi² = 4.41, df = 3 (P = 0.22), I² = 32.0%								



Analysis 1.3. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 3: Head growth (cm/week)

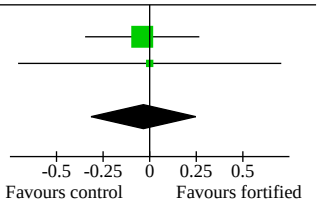
Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 All trials								
Modanlou 1986	1.09	0.07	8	0.82	0.24	10	3.2%	0.27 [0.11 , 0.43]
Gross 1987 (2)	0.84	0.21	17	0.84	0.09	9	5.8%	0.00 [-0.12 , 0.12]
Gross 1987 (1)	0.92	0.09	10	0.83	0.16	10	6.0%	0.09 [-0.02 , 0.20]
Polberger 1989	1.11	0.13	7	0.94	0.25	7	1.8%	0.17 [-0.04 , 0.38]
Porcelli 1992	0.7	0.3	10	0.7	0.2	10	1.6%	0.00 [-0.22 , 0.22]
Lucas 1996	1.01	0.47	137	0.95	0.35	138	8.1%	0.06 [-0.04 , 0.16]
Wauben 1998	1	0.1	12	0.9	0.2	13	5.2%	0.10 [-0.02 , 0.22]
Mukhopadhyay 2007	0.83	0.2	82	0.75	0.2	75	19.9%	0.08 [0.02 , 0.14]
Einloft 2015	0.91	0.21	19	0.98	0.14	19	6.0%	-0.07 [-0.18 , 0.04]
Gupta 2018	0.97	0.19	75	0.9	0.2	73	19.7%	0.07 [0.01 , 0.13]
Adhisivam 2019	0.56	0.1	40	0.54	0.16	40	22.8%	0.02 [-0.04 , 0.08]
Subtotal (95% CI)			**417**			**404**	**100.0%**	**0.06 [0.03 , 0.08]**
Heterogeneity: Chi² = 17.26, df = 10 (P = 0.07); I² = 42%								
Test for overall effect: Z = 4.01 (P < 0.0001)								
1.3.2 Trials recruiting only very preterm or VLBW infants								
Modanlou 1986	1.09	0.07	8	0.82	0.24	10	6.3%	0.27 [0.11 , 0.43]
Polberger 1989	1.11	0.13	7	0.94	0.25	7	3.5%	0.17 [-0.04 , 0.38]
Mukhopadhyay 2007	0.83	0.2	82	0.75	0.2	75	39.3%	0.08 [0.02 , 0.14]
Einloft 2015	0.91	0.21	19	0.98	0.14	19	12.0%	-0.07 [-0.18 , 0.04]
Gupta 2018	0.97	0.19	75	0.9	0.2	73	39.0%	0.07 [0.01 , 0.13]
Subtotal (95% CI)			**191**			**184**	**100.0%**	**0.07 [0.03 , 0.11]**
Heterogeneity: Chi² = 13.08, df = 4 (P = 0.01); I² = 69%								
Test for overall effect: Z = 3.66 (P = 0.0003)								
1.3.3 Trials conducted in low- or middle-income countries								
Mukhopadhyay 2007	0.83	0.2	82	0.75	0.2	75	29.0%	0.08 [0.02 , 0.14]
Einloft 2015	0.91	0.21	19	0.98	0.14	19	8.8%	-0.07 [-0.18 , 0.04]
Gupta 2018	0.97	0.19	75	0.9	0.2	73	28.8%	0.07 [0.01 , 0.13]
Adhisivam 2019	0.56	0.1	40	0.54	0.16	40	33.3%	0.02 [-0.04 , 0.08]
Subtotal (95% CI)			**216**			**207**	**100.0%**	**0.04 [0.01 , 0.08]**
Heterogeneity: Chi² = 6.45, df = 3 (P = 0.09); I² = 53%								
Test for overall effect: Z = 2.55 (P = 0.01)								
1.3.4 Trials using preterm formula powder as fortifier								
Gross 1987 (2)	0.84	0.21	17	0.84	0.09	9	22.8%	0.00 [-0.12 , 0.12]
Gupta 2018	0.97	0.19	75	0.9	0.2	73	77.2%	0.07 [0.01 , 0.13]
Subtotal (95% CI)			**92**			**82**	**100.0%**	**0.05 [-0.00 , 0.11]**
Heterogeneity: Chi² = 1.08, df = 1 (P = 0.30); I² = 8%								
Test for overall effect: Z = 1.92 (P = 0.06)								
Test for subgroup differences: Chi² = 1.25, df = 3 (P = 0.74), I² = 0%								



Analysis 1.4. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 4: Weight at 12 to 18 months (kg)

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
Lucas 1996	10.05	1.34	125	10.09	1.1	120	84.2%	-0.04 [-0.35 , 0.27]
Wauben 1998	9	0.9	12	9	0.9	13	15.8%	0.00 [-0.71 , 0.71]
Total (95% CI)			**137**			**133**	**100.0%**	**-0.03 [-0.31 , 0.25]**

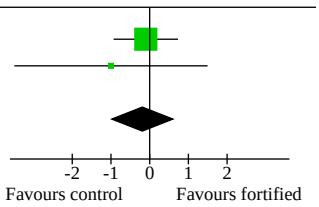
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 5: Length at 12 to 18 months (cm)

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
Lucas 1996	80	3.35	125	80.1	3.29	120	90.0%	-0.10 [-0.93 , 0.73]
Wauben 1998	74.9	3.7	12	75.9	2.5	13	10.0%	-1.00 [-3.50 , 1.50]
Total (95% CI)			**137**			**133**	**100.0%**	**-0.19 [-0.98 , 0.60]**

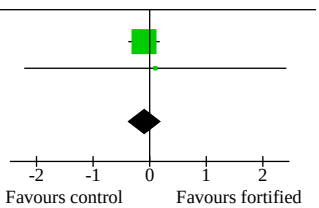
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 6: Head circumference at 12 to 18 months (cm)

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
Lucas 1996	48	1.12	125	48.1	1.1	120	98.6%	-0.10 [-0.38 , 0.18]
Wauben 1998	46.9	3.9	12	46.8	1.3	13	1.4%	0.10 [-2.22 , 2.42]
Total (95% CI)			**137**			**133**	**100.0%**	**-0.10 [-0.37 , 0.18]**

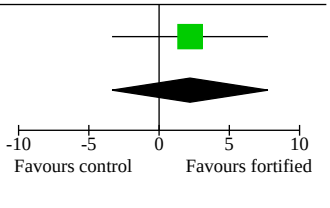
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 7: Mental development index at 18 months

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
Lucas 1996	106	22.4	125	103.8	21.9	120	100.0%	2.20 [-3.35 , 7.75]
Total (95% CI)			**125**			**120**	**100.0%**	**2.20 [-3.35 , 7.75]**

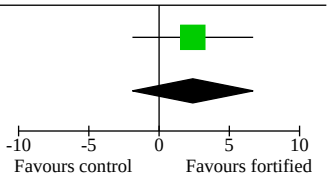
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 8: Psychomotor development index at 18 months

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
Lucas 1996	92.3	17.9	125	89.9	16.4	120	100.0%	2.40 [-1.90 , 6.70]
Total (95% CI)			**125**			**120**	**100.0%**	**2.40 [-1.90 , 6.70]**

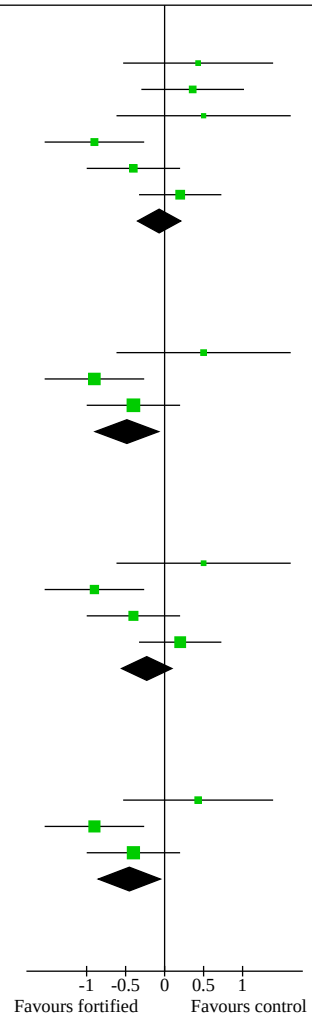
Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 9: Length of hospital stay (weeks)

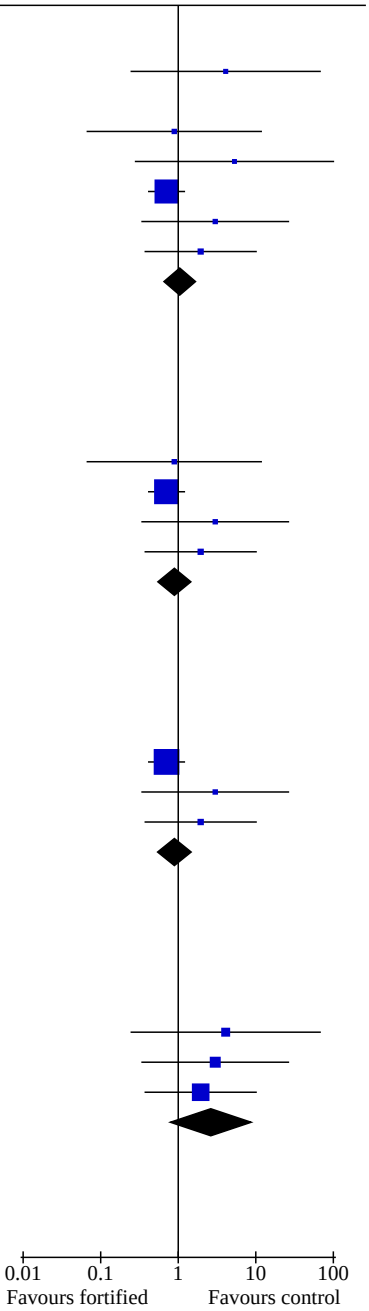
Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 All trials								
Zuckerman 1994	7.86	2	29	7.43	1.57	24	8.3%	0.43 [-0.53 , 1.39]
Mukhopadhyay 2007	4.56	2.31	82	4.2	1.89	75	17.7%	0.36 [-0.30 , 1.02]
Einloft 2015	5.2	1.6	19	4.7	1.9	19	6.2%	0.50 [-0.62 , 1.62]
El Sakka 2016	3.2	1.2	25	4.1	1.1	25	18.8%	-0.90 [-1.54 , -0.26]
Gupta 2018	5	1.7	75	5.4	2	73	21.4%	-0.40 [-1.00 , 0.20]
Adhisivam 2019	2.2	1.1	40	2	1.3	40	27.6%	0.20 [-0.33 , 0.73]
Subtotal (95% CI)			**270**			**256**	**100.0%**	**-0.07 [-0.35 , 0.21]**
Heterogeneity: Chi² = 12.35, df = 5 (P = 0.03); I² = 60%								
Test for overall effect: Z = 0.49 (P = 0.62)								
1.9.2 Trials recruiting only very preterm or VLBW infants								
Einloft 2015	5.2	1.6	19	4.7	1.9	19	13.3%	0.50 [-0.62 , 1.62]
El Sakka 2016	3.2	1.2	25	4.1	1.1	25	40.6%	-0.90 [-1.54 , -0.26]
Gupta 2018	5	1.7	75	5.4	2	73	46.1%	-0.40 [-1.00 , 0.20]
Subtotal (95% CI)			**119**			**117**	**100.0%**	**-0.48 [-0.89 , -0.08]**
Heterogeneity: Chi² = 4.69, df = 2 (P = 0.10); I² = 57%								
Test for overall effect: Z = 2.33 (P = 0.02)								
1.9.3 Trials conducted in low- or middle-income countries								
Einloft 2015	5.2	1.6	19	4.7	1.9	19	8.3%	0.50 [-0.62 , 1.62]
El Sakka 2016	3.2	1.2	25	4.1	1.1	25	25.5%	-0.90 [-1.54 , -0.26]
Gupta 2018	5	1.7	75	5.4	2	73	28.9%	-0.40 [-1.00 , 0.20]
Adhisivam 2019	2.2	1.1	40	2	1.3	40	37.3%	0.20 [-0.33 , 0.73]
Subtotal (95% CI)			**159**			**157**	**100.0%**	**-0.23 [-0.55 , 0.09]**
Heterogeneity: Chi² = 8.74, df = 3 (P = 0.03); I² = 66%								
Test for overall effect: Z = 1.39 (P = 0.16)								
1.9.4 Trials using preterm formula powder as fortifier								
Zuckerman 1994	7.86	2	29	7.43	1.57	24	17.1%	0.43 [-0.53 , 1.39]
El Sakka 2016	3.2	1.2	25	4.1	1.1	25	38.8%	-0.90 [-1.54 , -0.26]
Gupta 2018	5	1.7	75	5.4	2	73	44.1%	-0.40 [-1.00 , 0.20]
Subtotal (95% CI)			**129**			**122**	**100.0%**	**-0.45 [-0.85 , -0.05]**
Heterogeneity: Chi² = 5.16, df = 2 (P = 0.08); I² = 61%								
Test for overall effect: Z = 2.23 (P = 0.03)								

Test for subgroup differences: Chi² = 3.90, df = 3 (P = 0.27), I² = 23.1%



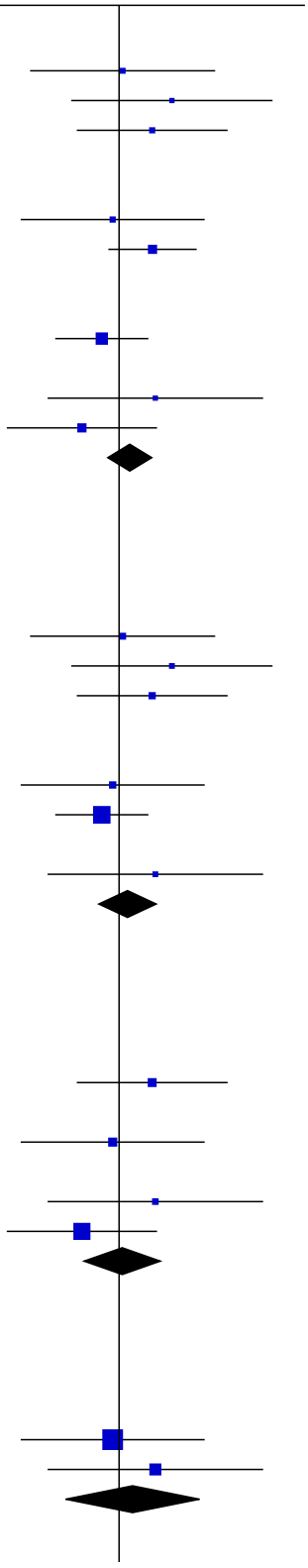
Analysis 1.10. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 10: Feed intolerance

Study or Subgroup	Fortified Events	Fortified Total	Unfortified Events	Unfortified Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 All trials						
Gross 1987 (2)	4	21	0	9	2.4%	4.09 [0.24 , 68.94]
Gross 1987 (1)	0	10	0	10		Not estimable
Polberger 1989	1	9	1	8	3.7%	0.89 [0.07 , 12.00]
Wauben 1998	2	15	0	16	1.7%	5.31 [0.28 , 102.38]
Mukhopadhyay 2007	17	82	22	75	81.4%	0.71 [0.41 , 1.23]
El Sakka 2016	3	25	1	25	3.5%	3.00 [0.33 , 26.92]
Gupta 2018	4	75	2	73	7.2%	1.95 [0.37 , 10.30]
Subtotal (95% CI)		**237**		**216**	**100.0%**	**1.05 [0.65 , 1.67]**
Total events:	31		26			
Heterogeneity: Chi² = 5.44, df = 5 (P = 0.36); I² = 8%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.10.2 Trials recruiting only very preterm or VLBW infants						
Polberger 1989	1	9	1	8	3.9%	0.89 [0.07 , 12.00]
Mukhopadhyay 2007	17	82	22	75	84.9%	0.71 [0.41 , 1.23]
El Sakka 2016	3	25	1	25	3.7%	3.00 [0.33 , 26.92]
Gupta 2018	4	75	2	73	7.5%	1.95 [0.37 , 10.30]
Subtotal (95% CI)		**191**		**181**	**100.0%**	**0.89 [0.55 , 1.45]**
Total events:	25		26			
Heterogeneity: Chi² = 2.70, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
1.10.3 Trials conducted in low- or middle-income countries						
Mukhopadhyay 2007	17	82	22	75	88.4%	0.71 [0.41 , 1.23]
El Sakka 2016	3	25	1	25	3.8%	3.00 [0.33 , 26.92]
Gupta 2018	4	75	2	73	7.8%	1.95 [0.37 , 10.30]
Subtotal (95% CI)		**182**		**173**	**100.0%**	**0.89 [0.54 , 1.47]**
Total events:	24		25			
Heterogeneity: Chi² = 2.70, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.10.4 Trials using preterm formula powder as fortifier						
Gross 1987 (2)	4	21	0	9	18.5%	4.09 [0.24 , 68.94]
El Sakka 2016	3	25	1	25	26.9%	3.00 [0.33 , 26.92]
Gupta 2018	4	75	2	73	54.6%	1.95 [0.37 , 10.30]
Subtotal (95% CI)		**121**		**107**	**100.0%**	**2.63 [0.79 , 8.71]**
Total events:	11		3			
Heterogeneity: Chi² = 0.23, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Chi² = 2.94, df = 3 (P = 0.40), I² = 0%						



Analysis 1.11. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 11: Necrotising enterocolitis

Study or Subgroup	Fortified Events	Fortified Total	Unfortified Events	Unfortified Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 All trials						
Faerk 2000	1	36	1	40	6.3%	1.11 [0.07 , 17.12]
Modanlou 1986	2	20	0	19	3.4%	4.76 [0.24 , 93.19]
Pettifor 1989	3	53	1	47	7.0%	2.66 [0.29 , 24.71]
Polberger 1989	0	7	0	7		Not estimable
Porcelli 1992	0	7	0	7		Not estimable
Zuckerman 1994	1	29	1	24	7.2%	0.83 [0.05 , 12.54]
Lucas 1996	8	137	3	138	19.8%	2.69 [0.73 , 9.91]
Wauben 1998	0	15	0	16		Not estimable
Nicholl 1999	0	13	0	10		Not estimable
Bhat 2003	3	50	5	50	33.1%	0.60 [0.15 , 2.38]
Mukhopadhyay 2007	0	82	0	75		Not estimable
Gupta 2018	1	75	0	73	3.4%	2.92 [0.12 , 70.56]
Adhisivam 2019	1	40	3	40	19.9%	0.33 [0.04 , 3.07]
Subtotal (95% CI)		**564**		**546**	**100.0%**	**1.37 [0.72 , 2.63]**
Total events:	20		14			
Heterogeneity: Chi² = 5.35, df = 7 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.11.2 Trials recruiting only very preterm or VLBW infants						
Faerk 2000	1	36	1	40	10.4%	1.11 [0.07 , 17.12]
Modanlou 1986	2	20	0	19	5.6%	4.76 [0.24 , 93.19]
Pettifor 1989	3	53	1	47	11.6%	2.66 [0.29 , 24.71]
Polberger 1989	0	7	0	7		Not estimable
Porcelli 1992	0	7	0	7		Not estimable
Zuckerman 1994	1	29	1	24	12.0%	0.83 [0.05 , 12.54]
Bhat 2003	3	50	5	50	54.8%	0.60 [0.15 , 2.38]
Mukhopadhyay 2007	0	82	0	75		Not estimable
Gupta 2018	1	75	0	73	5.6%	2.92 [0.12 , 70.56]
Subtotal (95% CI)		**359**		**342**	**100.0%**	**1.28 [0.55 , 2.99]**
Total events:	11		8			
Heterogeneity: Chi² = 2.70, df = 5 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.57)						
1.11.3 Trials conducted in low- or middle-income countries						
Pettifor 1989	3	53	1	47	18.7%	2.66 [0.29 , 24.71]
Porcelli 1992	0	7	0	7		Not estimable
Zuckerman 1994	1	29	1	24	19.3%	0.83 [0.05 , 12.54]
Mukhopadhyay 2007	0	82	0	75		Not estimable
Gupta 2018	1	75	0	73	9.0%	2.92 [0.12 , 70.56]
Adhisivam 2019	1	40	3	40	53.0%	0.33 [0.04 , 3.07]
Subtotal (95% CI)		**286**		**266**	**100.0%**	**1.10 [0.36 , 3.38]**
Total events:	6		5			
Heterogeneity: Chi² = 2.12, df = 3 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
1.11.4 Trials using preterm formula powder as fortifier						
Zuckerman 1994	1	29	1	24	68.4%	0.83 [0.05 , 12.54]
Gupta 2018	1	75	0	73	31.6%	2.92 [0.12 , 70.56]
Subtotal (95% CI)		**104**		**97**	**100.0%**	**1.49 [0.21 , 10.76]**
Total events:	2		1			
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%						

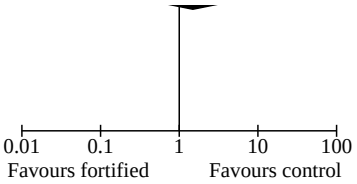


Analysis 1.11. (Continued)

Total events:	2	1

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

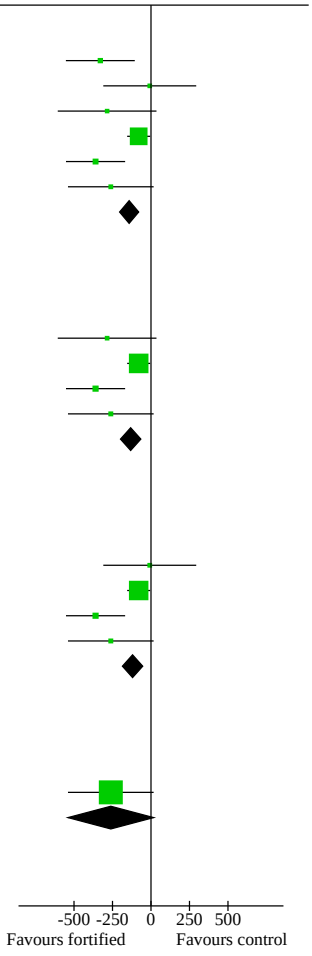
Test for subgroup differences: Chi² = 0.13, df = 3 (P = 0.99), I² = 0%



Analysis 1.12. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 12: Serum ALP (IU/L): restricted to trials without mineral supplementation of the control group

Study or Subgroup	Fortified Mean	Fortified SD	Fortified Total	Unfortified Mean	Unfortified SD	Unfortified Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 All trials								
Einloft 2015	391	177	19	720	465	19	7.7%	-329.00 [-552.72 , -105.28]
Gathwala 2012	711	646	30	719	542	30	4.2%	-8.00 [-309.75 , 293.75]
Modanlou 1986	790	202	7	1075	434	9	3.7%	-285.00 [-605.61 , 35.61]
Mukhopadhyay 2007	556	231	82	636	245	75	69.0%	-80.00 [-154.66 , -5.34]
Pettifor 1989	483	152	29	843	514	30	10.4%	-360.00 [-552.07 , -167.93]
Zuckerman 1994	620	368	18	881	435	15	5.0%	-261.00 [-539.14 , 17.14]
Subtotal (95% CI)			**185**			**178**	**100.0%**	**-141.93 [-203.93 , -79.92]**
Heterogeneity: Chi² = 12.51, df = 5 (P = 0.03); I² = 60%								
Test for overall effect: Z = 4.49 (P < 0.00001)								
1.12.2 Trials recruiting only very preterm or VLBW infants								
Modanlou 1986	790	202	7	1075	434	9	4.2%	-285.00 [-605.61 , 35.61]
Mukhopadhyay 2007	556	231	82	636	245	75	78.3%	-80.00 [-154.66 , -5.34]
Pettifor 1989	483	152	29	843	514	30	11.8%	-360.00 [-552.07 , -167.93]
Zuckerman 1994	620	368	18	881	435	15	5.6%	-261.00 [-539.14 , 17.14]
Subtotal (95% CI)			**136**			**129**	**100.0%**	**-132.03 [-198.09 , -65.98]**
Heterogeneity: Chi² = 8.98, df = 3 (P = 0.03); I² = 67%								
Test for overall effect: Z = 3.92 (P < 0.0001)								
1.12.3 Trials conducted in low- or middle-income countries								
Gathwala 2012	711	646	30	719	542	30	4.8%	-8.00 [-309.75 , 293.75]
Mukhopadhyay 2007	556	231	82	636	245	75	77.9%	-80.00 [-154.66 , -5.34]
Pettifor 1989	483	152	29	843	514	30	11.8%	-360.00 [-552.07 , -167.93]
Zuckerman 1994	620	368	18	881	435	15	5.6%	-261.00 [-539.14 , 17.14]
Subtotal (95% CI)			**159**			**150**	**100.0%**	**-119.66 [-185.54 , -53.78]**
Heterogeneity: Chi² = 8.62, df = 3 (P = 0.03); I² = 65%								
Test for overall effect: Z = 3.56 (P = 0.0004)								
1.12.4 Trials using preterm formula powder as fortifier								
Zuckerman 1994	620	368	18	881	435	15	100.0%	-261.00 [-539.14 , 17.14]
Subtotal (95% CI)			**18**			**15**	**100.0%**	**-261.00 [-539.14 , 17.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								

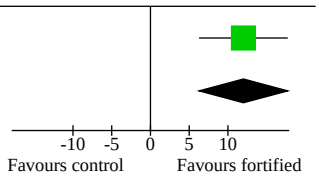
Test for subgroup differences: Chi² = 1.05, df = 3 (P = 0.79), I² = 0%



Analysis 1.13. Comparison 1: Fortified breast milk versus unfortified breast milk, Outcome 13: Bone mineral content (mg/cm): restricted to trials without mineral supplementation of the control group

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Pettifor 1989	59	13	29	47	9	30	100.0%	12.00 [6.28 , 17.72]
Total (95% CI)			**29**			**30**	**100.0%**	**12.00 [6.28 , 17.72]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.11 (P < 0.0001)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategy

Cochrane Central Register of Controlled Trials (CENTRAL)

Wiley http://onlinelibrary.wiley.com/

Issue 9 of 12, September 2019

Searched on: 26th September 2019

Records retrieved: 714

#1 MeSH descriptor: [Infant, Newborn] explode all trees 15243

#2 MeSH descriptor: [Premature Birth] this term only 1155

#3 (neonat* or neo next nat*):ti,ab,kw 20707

#4 (newborn* or new next born* or newly next born*):ti,ab,kw 26166

#5 (preterm or preterms or pre next term or pre next terms):ti,ab,kw 12761

#6 (preemie* or premie or premies):ti,ab,kw 44

#7 (prematur* near/3 (birth* or born or deliver*)):ti,ab,kw 2481

#8 (low near/3 (birthweight* or birth next weight*)):ti,ab,kw 5297

#9 (lbw or vlbw or elbw):ti,ab,kw 1576

#10 infan*:ti,ab,kw 58312

#11 (baby or babies):ti,ab,kw 7655

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 73825

#13 MeSH descriptor: [Milk, Human] this term only 959

#14 MeSH descriptor: [Milk Banks] this term only 5

#15 MeSH descriptor: [Breast Milk Expression] this term only 24

#16 #13 or #14 or #15 972

#17 MeSH descriptor: [Food, Fortified] this term only 1362

#18 MeSH descriptor: [Dietary Supplements] this term only 9483

#19 #17 or #18 10677

#20 #16 and #19 273

#21 (fortif* near/4 ((human* or breast or express*) near/2 milk*)):ti,ab,kw 271

#22 (fortif* near/4 ((mother* or maternal or donor* or donat* or bank*) near/2 milk*)):ti,ab,kw 55

#23 (supplement* near/4 ((human* or breast or express*) near/2 milk*)):ti,ab,kw 279

#24 (supplement* near/4 ((mother* or maternal or donor* or donat* or bank*) near/2 milk*)):ti,ab,kw 70

#25 (enrich* near/4 ((human* or breast or express*) near/2 milk*)):ti,ab,kw 37

#26 (enrich* near/4 ((mother* or maternal or donor* or donat* or bank*) near/2 milk*)):ti,ab,kw 7

#27 ((fortif* or supplement* or enrich*) near/4 DHM):ti,ab,kw 3

#28 ((fortif* or supplement* or enrich*) near/4 HM):ti,ab,kw 39

#29 ((fortif* or supplement* or enrich*) near/4 breastmilk*):ti,ab,kw 30

#30 ((fortif* or supplement* or enrich*) near/3 (multinutrient* or multi next nutrient* or multicomponent* or multi next component*)):ti,ab,kw 106

#31 ((supplement* or enrich*) near/3 (bovine* or cow* or donkey*) near/3 milk*):ti,ab,kw 54

#32 (fortif* near/5 (bovine* or cow* or donkey*)):ti,ab,kw 64

#33 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 758

#34 #20 or #33 904

#35 #12 and #34 734

#36 #12 and #34 in Trials 714

MEDLINE ALL

(includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)

OvidSP http://ovidsp.ovid.com/

1946 to September 24, 2019

Searched on: 26th September 2019

Records retrieved: 735

1 exp Infant, Newborn/ (590174)

2 Premature Birth/ (12627)

3 (neonat$ or neo nat$).ti,ab. (252905)

4 (newborn$ or new born$ or newly born$).ti,ab. (160734)

5 (preterm or preterms or pre term or pre terms).ti,ab. (70462)

6 (preemie$ or premie or premies).ti,ab. (164)

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (15050)

8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (33172)

9 (lbw or vlbw or elbw).ti,ab. (7969)

10 infan$.ti,ab. (420915)

11 (baby or babies).ti,ab. (67489)

12 or/1-11 (1021962)

13 Milk, Human/ (18549)

14 Milk Banks/ (461)

15 Breast Milk Expression/ (271)

16 13 or 14 or 15 (18750)

17 Food, Fortified/ (9079)

18 Dietary Supplements/ (53248)

19 17 or 18 (61296)

20 16 and 19 (894)

21 (fortif$ adj4 ((human$ or breast or express$) adj2 milk$)).ti,ab. (549)

22 (fortif$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).ti,ab. (96)

23 (supplement$ adj4 ((human$ or breast or express$) adj2 milk$)).ti,ab. (460)

24 (supplement$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).ti,ab. (107)

25 (enrich$ adj4 ((human$ or breast or express$) adj2 milk$)).ti,ab. (90)

26 (enrich$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).ti,ab. (15)

27 ((fortif$ or supplement$ or enrich$) adj4 DHM).ti,ab. (18)

28 ((fortif$ or supplement$ or enrich$) adj4 HM).ti,ab. (114)

29 ((fortif$ or supplement$ or enrich$) adj4 breastmilk$).ti,ab. (47)

30 ((fortif$ or supplement$ or enrich$) adj3 (multinutrient$ or multi-nutrient$ or multicomponent$ or multi-component$)).ti,ab. (152)

31 ((supplement$ or enrich$) adj3 (bovine$ or cow$ or donkey$) adj3 milk$).ti,ab. (228)

32 (fortif$ adj5 (bovine$ or cow$ or donkey$)).ti,ab. (229)

33 or/21-32 (1727)

34 20 or 33 (2236)

35 12 and 34 (1663)

36 randomised controlled trial.pt. (489981)

37 controlled clinical trial.pt. (93266)

38 randomized.ab. (454848)

39 placebo.ab. (200736)

40 drug therapy.fs. (2141859)

41 randomly.ab. (318352)

42 trial.ab. (476880)

43 groups.ab. (1955276)

44 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 (4527911)

45 exp animals/ not humans.sh. (4618767)

46 44 not 45 (3919813)

47 35 and 46 (735)

Embase

OvidSP http://ovidsp.ovid.com/

1974 to 2019 September 25

Searched on: 26th September 2019

Records retrieved: 978

1 newborn/ (510070)

2 prematurity/ (97287)

3 exp low birth weight/ (59374)

4 (neonat$ or neo nat$).ti,ab. (328678)

5 (newborn$ or new born$ or newly born$).ti,ab. (186945)

6 (preterm or preterms or pre term or pre terms).ti,ab. (99681)

7 (preemie$ or premie or premies).ti,ab. (249)

8 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (20715)

9 (low adj3 (birthweight$ or birth weight$)).ti,ab. (41955)

10 (lbw or vlbw or elbw).ti,ab. (10924)

11 infan$.ti,ab. (480027)

12 (baby or babies).ti,ab. (93471)

13 or/1-12 (1102074)

14 breast milk/ (26236)

15 milk banks/ (172)

16 donor milk/ (96)

17 breast milk expression/ (319)

18 or/14-17 (26483)

19 fortified food/ (923)

20 diet supplementation/ (83893)

21 dietary supplement/ (10128)

22 exp nutrition supplement/ (14952)

23 mineral supplementation/ (1534)

24 vitamin supplementation/ (31158)

25 or/19-24 (137963)

26 18 and 25 (1662)

27 (fortif$ adj4 ((human$ or breast or express$) adj2 milk$)).ti,ab. (767)

28 (fortif$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).ti,ab. (131)

29 (supplement$ adj4 ((human$ or breast or express$) adj2 milk$)).ti,ab. (559)

30 (supplement$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).ti,ab. (130)

31 (enrich$ adj4 ((human$ or breast or express$) adj2 milk$)).ti,ab. (118)

32 (enrich$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).ti,ab. (17)

33 ((fortif$ or supplement$ or enrich$) adj4 DHM).ti,ab. (23)

34 ((fortif$ or supplement$ or enrich$) adj4 HM).ti,ab. (164)

35 ((fortif$ or supplement$ or enrich$) adj4 breastmilk$).ti,ab. (59)

36 ((fortif$ or supplement$ or enrich$) adj3 (multinutrient$ or multi-nutrient$ or multicomponent$ or multi-component$)).ti,ab. (203)

37 ((supplement$ or enrich$) adj3 (bovine$ or cow$ or donkey$) adj3 milk$).ti,ab. (274)

38 (fortif$ adj5 (bovine$ or cow$ or donkey$)).ti,ab. (306)

39 or/27-38 (2244)

40 26 or 39 (3544)

41 13 and 40 (2587)

42 randomised controlled trial/ (573423)

43 controlled clinical trial/ (465486)

44 42 or 43 (759228)

45 Random$.ti,ab. (1463071)

46 randomizations/ (84472)

47 intermethod comparison/ (254409)

48 placebo.ti,ab. (296225)

49 (compare or compared or comparison).ti. (492537)

50 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (1997679)

51 (open adj label).ti,ab. (74701)

52 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (224895)

53 double blind procedure/ (166551)

54 parallel group$1.ti,ab. (24383)

55 (crossover or cross over).ti,ab. (100855)

56 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab. (315479)

57 (assigned or allocated).ti,ab. (370048)

58 (controlled adj7 (study or design or trial)).ti,ab. (331556)

59 (volunteer or volunteers).ti,ab. (239725)

60 human experiment/ (469138)

61 trial.ti. (282787)

62 or/44-61 (4781482)

63 41 and 62 (978)

CINAHL Complete

via EBSCO http://www.ebsco.com/

Inception to 25th September 2019

Searched on: 26th September 2019

Records retrieved: 33

S57	S31 AND S56	371
S56	S47 OR S55	1,085,472
S55	S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54	824,161
S54	TI before N3 after OR AB before N3 after	66,639
S53	(MH "Controlled Before-After Studies")	128
S52	TI (multicentre* or multi-centre* or multicenter* or multi-center*) OR AB (multicentre* or multi-centre* or multicenter* or multi-center*)	44,660
S51	(MH "Multicenter Studies")	140,466
S50	TI assign* OR AB assign*	66,850
S49	TI (group or groups) OR AB (group or groups)	644,433
S48	(MH "Control Group")	11,172
S47	S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46	622,565
S46	AB (cluster W3 RCT)	301
S45	MH (crossover design) OR MH (comparative studies)	233,540
S44	AB (control W5 group)	94,252
S43	PT (randomised controlled trial)	86,755
S42	MH (placebos)	11,452
S41	MH (sample size) AND AB (assigned OR allocated OR control)	3,698
S40	TI trial	95,074
S39	AB random*	268,743
S38	TI randomised OR randomised	93,017
S37	(MH "Cluster Sample")	3,883
S36	(MH "Pretest-Posttest Design")	39,135
S35	(MH "Random Assignment")	56,283

(Continued)

S34	(MH "Single-Blind Studies")	12,796
S33	(MH "Double-Blind Studies")	42,482
S32	(MH "Randomized Controlled Trials")	86,398
S31	S13 AND S30	787
S30	S16 OR S29	989
S29	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	589
S28	TI ((supplement* or enrich*) N3 (bovine* or cow* or donkey*) N3 milk*)) OR AB ((supplement* or enrich*) N3 (bovine* or cow* or donkey*) N3 milk*))	40
S27	TI ((fortif* or supplement* or enrich*) N3 (multinutrient* or multi-nutrient* or multicomponent* or multi-component*)) OR AB ((fortif* or supplement* or enrich*) N3 (multinutrient* or multi-nutrient* or multicomponent* or multi-component*))	71
S26	TI ((fortif* N5 (bovine* or cow* or donkey*))) OR AB ((fortif* N5 (bovine* or cow* or donkey*)))	47
S25	TI (((fortif* or supplement* or enrich*) N4 breastmilk*)) OR AB (((fortif* or supplement* or enrich*) N4 breastmilk*))	14
S24	TI (((fortif* or supplement* or enrich*) N4 HM)) OR AB (((fortif* or supplement* or enrich*) N4 HM))	26
S23	TI (((fortif* or supplement* or enrich*) N4 DHM)) OR AB (((fortif* or supplement* or enrich*) N4 DHM))	8
S22	TI ((enrich* N4 ((mother* or maternal or donor* or donat* or bank*) N2 milk*))) OR AB ((enrich* N4 ((mother* or maternal or donor* or donat* or bank*) N2 milk*)))	5
S21	TI ((enrich* N4 ((human* or breast or express*) N2 milk*))) OR AB ((enrich* N4 ((human* or breast or express*) N2 milk*)))	23
S20	TI ((supplement* N4 ((mother* or maternal or donor* or donat* or bank*) N2 milk*))) OR AB ((supplement* N4 ((mother* or maternal or donor* or donat* or bank*) N2 milk*)))	49
S19	TI ((supplement* N4 ((human* or breast or express*) N2 milk*))) OR AB ((supplement* N4 ((human* or breast or express*) N2 milk*)))	169
S18	TI ((fortif* N4 ((mother* or maternal or donor* or donat* or bank*) N2 milk*))) OR AB ((fortif* N4 ((mother* or maternal or donor* or donat* or bank*) N2 milk*)))	35
S17	TI ((fortif* N4 ((human* or breast or express*) N2 milk*))) OR AB ((fortif* N4 ((human* or breast or express*) N2 milk*)))	255
S16	S14 AND S15	582

(Continued)

S15	(MH "Food, Fortified") or (MH "Dietary Supplements") or (MH "Dietary Supplementation") or (MH "Infant Feeding, Supplemental")	39,564
S14	(MH "Milk, Human+") or (MH "Milk Expression") or (MH "Milk Banks")	5,692
S13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	223,811
S12	TI (baby or babies) OR AB (baby or babies)	27,781
S11	TI infan* OR AB infan*	96,039
S10	TI (lbw or vlbw or elbw) OR AB (lbw or vlbw or elbw)	2,827
S9	TI (low N3 (birthweight* or birth-weight*)) OR AB (low N3 (birthweight* or birth-weight*))	10,367
S8	TI (prematur* N3 (birth* or born or deliver*)) OR AB (prematur* N3 (birth* or born or deliver*))	3,897
S7	TI (preemie* or premie or premies) OR AB (preemie* or premie or premies)	280
S6	TI (preterm or preterms or pre-term or pre-terms) OR AB (preterm or preterms or pre-term or pre-terms)	27,710
S5	TI (newborn* or new-born* or newly N1 born*) OR AB (newborn* or new-born* or newly N1 born*)	26,361
S4	TI (neonat* or neo-nat*) OR AB (neonat* or neo-nat*)	56,313
S3	MH "Infant, Premature"	20,206
S2	MH "Infant, Low Birth Weight+"	12,383
S1	MH "Infant, Newborn+"	122,798

Maternity and Infant Care

OvidSP http://ovidsp.ovid.com/

1971 to August 2019

Searched on: 26th September 2019

Records retrieved: 371

1 (fortif$ adj4 ((human$ or breast or express$) adj2 milk$)).mp. (251)

2 (fortif$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).mp. (39)

3 (supplement$ adj4 ((human$ or breast or express$) adj2 milk$)).mp. (165)

4 (supplement$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).mp. (44)

5 (enrich$ adj4 ((human$ or breast or express$) adj2 milk$)).mp. (14)

6 (enrich$ adj4 ((mother$ or maternal or donor$ or donat$ or bank$) adj2 milk$)).mp. (4)

7 ((fortif$ or supplement$ or enrich$) adj4 DHM).mp. (5)

8 ((fortif$ or supplement$ or enrich$) adj4 HM).mp. (22)

9 ((fortif$ or supplement$ or enrich$) adj4 breastmilk$).mp. (21)

10 ((fortif$ or supplement$ or enrich$) adj3 (multinutrient$ or multi-nutrient$ or multicomponent$ or multi-component$)).mp. (24)

11 ((supplement$ or enrich$) adj3 (bovine$ or cow$ or donkey$) adj3 milk$).mp. (12)

12 (fortif$ adj5 (bovine$ or cow$ or donkey$)).mp. (31)

13 or/1-12 (484)

Search filters to limit retrieval to randomised controlled trials were applied in MEDLINE (Lefebvre 2011), Embase (https://www.cochranelibrary.com/central/central-creation) and CINAHL (Glanville 2019).

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 30th September 2019

Records retrieved: 237

The following search strings were entered into the advanced search screen:

1. 59 Studies found for: (milk OR breastmilk) AND (fortify OR fortifying OR fortified OR fortifies OR fortifier) | Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR newborn

2. 161 Studies found for: (milk OR breastmilk) AND (supplement OR supplements OR supplemented OR supplementing OR supplementation) | Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR newborn

3. 13 Studies found for: (milk OR breastmilk) AND (enrich OR enriched OR enrichment OR enriching) | Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR newborn

4. 4 Studies found for: (multinutrient OR multi-nutrient OR multicomponent OR multi-component) AND (milk OR breastmilk) | Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR newborn

WHO International Clinical Trials Registry Platform (ICTRP)

http://apps.who.int/trialsearch/

Searched on: 30th September 2019

Records retrieved: 101

The following search strings were entered into the advanced search screen:

1. 37 records for 36 trials

CONDITION: Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR neo-nate OR neonatal OR neo-natal OR newborn

INTERVENTION: fortif AND milk

2. 54 records for 54 trials

CONDITION: Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR neo-nate OR neonatal OR neo-natal OR newborn

INTERVENTION: supplement AND milk

3. 9 records for 9 trials

CONDITION: Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR neo-nate OR neonatal OR neo-natal OR newborn

INTERVENTION: enrich AND milk

4. 2 records for 2 trials

CONDITION: Preterm OR pre-term OR premature OR prematurity OR preemie OR premie OR low birth weight OR low birthweight OR LBW OR VLBW OR ELBW OR neonate OR neo-nate OR neonatal

INTERVENTION: multinutrient OR multi-nutrient OR multicomponent

Appendix 2. Risk of bias

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk, or unclear risk for participants; and
- low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared pre-specified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (when it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (when not all of the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design, whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

Appendix 3. GRADE

GRADE considers that evidence from randomised controlled trials is of high certainty, but that assessment may be downgraded based on consideration of any of five areas.

- Design (risk of bias).
- Consistency across studies.
- Directness of evidence.
- Precision of estimates.
- Presence of publication bias.

This results in an assessment of the certainty of a body of evidence in one of four grades.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

WHAT'S NEW

Date	Event	Description
7 July 2020	Amended	Information regarding The Gerber Foundation added to Declarations of interest section

HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 4, 1998

Date	Event	Description
24 April 2020	New citation required but conclusions have not changed	The updated review includes 4 new studies, but the conclusions remain unchanged.
24 April 2020	New search has been performed	This review updates "Multicomponent fortified human milk for promoting growth in preterm infants," published in the Cochrane Library, Issue 11, 2003.
29 August 2003	New search has been performed	This review updates the existing review titled, "Multicomponent fortified human milk for promoting growth in preterm infants", published in the Cochrane Library, Issue 4, 1998 This review presents 6 new studies (included - Zuckerman, Nicholl, Faerk; excluded - Gupta, Porcelli, Reiss) and 1 follow-up report (Wauben)

CONTRIBUTIONS OF AUTHORS

Jennifer Brown, Luling Lin, and William McGuire screened and appraised reports identified in the updated search, extracted and analysed data from included studies, and drafted the review. Nick Embleton and Jane Harding arbitrated inclusion and data extraction disagreements and drafted the review.

DECLARATIONS OF INTEREST

JVEB: nothing to declare.

LL: nothing to declare.

NDE declares the following: receiving a research grant award for a randomised controlled trial of breast milk products from Prolacta Bioscience, 2017; receiving a grant from Danone Early Life Nutrition to support a study on feeding in late and moderately preterm infants, 2018; receiving a grant from Nestle Nutrition for transcriptomic analyses of gut tissue, 2016; and presenting lectures with Wyeth Nutrition in 2017, Nestle Nutrition Institute in 2017 and 2018, Philipps in 2017, and Fresenius in 2017.

JH: nothing to declare.

WM: nothing to declare.

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- Vermont Oxford Network, USA

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- The Gerber Foundation, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We defined a "multi-nutrient" fortifier as one that contains both protein and non-protein energy (carbohydrate or fat) with the option of including other nutrients, such as minerals, vitamins, or electrolytes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Food, Fortified; *Infant Nutritional Physiological Phenomena; Infant, Premature [*growth & development]; Milk, Human [*chemistry]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn